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THE INTERNATIONAL UNION AGAINST TUBERCULOSIS

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Control of epidemic diseases has been a matter of international concern for centuries. Quarantine was and still is the official protective measure employed. While not perfect, it plays a large part in circumscribing sporadic outbreaks of the more virulent infections. Prior to the recent war the Public Health Division of the League of Nations at Geneva maintained a statistical bureau which received daily cables from stations throughout the world, reporting all cases of diseases such as cholera, yellow fever, plague, typhus and the like. This enabled the quarantine principle to reach a high level of efficiency.

Tuberculosis, the most wide-spread of communicable diseases, has profited little from the application of this principle and that only in very recent years. Migration of the tuberculous is still but mildly impeded by national regulations or international agreements. The reasons for this contrast between tuberculosis and the more swiftly lethal pestilences need not detain us. Sir Robert Philip's teaching that control of tuberculosis is a responsibility of the people summarizes the situation. Cholera and yellow fever dramatize themselves and lead to instant popular demand for governmental action. Not so with the insidious attack of the *Mycobacterium tuberculosis*. Here health education must be worked, based on interchange of world experience and research.

In the "Nineties" Germany recognized this need. The Central International Bureau for the Prevention of Consumption was organized in Berlin. This was the forerunner of the present International Union, although the latter was organized *de novo* after the first world war, subsequent to a refusal on the part of England, France and The U.S.A. to continue their memberships in that organization, which then passed out of existence. It is not unfair to state, however, that this original organization with its biennial international conferences had demonstrated the value of such an agency.

Preliminary discussions looking toward the development of an International Union against Tuberculosis arose during a meeting of the National Association for the Prevention of Tuberculosis in London in the autumn of 1919. Our delegates to that meeting were Dr. Charles J. Hatfield, Dr. David R. Lyman and Dr. William Charles White, while Dr. Leon Bernard and Dr. Edouard Rist represented France. Subsequent conferences with Sir Robert Philip and with M. Léon Bourgeois, who had been Chairman of the extinct International Conference on Tuberculosis, led to an agreement that Mr. Bourgeois should send formal invitations to the national tuberculosis associations of England, France, Italy and the United States to appoint delegates to an organization meeting in Paris in 1920.

The meeting took place, the United States being represented by a number of

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physicians and laymen. Organization of an International Union against Tuberculosis was completed and a constitution adopted, providing for the election of officers, a directing Council and an Executive Committee. The Council has representatives from each of the member states of the Union and the Executive Committee consists of not less than five elected members. Council members from the United States were Drs. James Alexander Miller, Gerald B. Webb, David R. Lyman, George E. Bushnell and Charles L. Minor. Dr. Webb was made a member of the Executive Committee. He was followed successively in that office by Dr. Farrand, Dr. Hatfield, Dr. Theobald Smith, Dr. E. L. Opic and the present Managing Director of our Association.

Such, in bare outline, was the origin of the International Union against Tuberculosis. It grew out of the conviction that an unofficial scientific body would be able, through periodic informal conferences, to advance world interest in tuberculosis research and the promotion of preventive measures for the control of this disease. In 1926, at the Washington Conference, the barriers preventing former enemy countries to adhere were withdrawn. Membership increased rapidly until at the outbreak of the second world war 44 countries or colonies were represented. Certain of these have voluntary associations like our own which represent their respective states. Others have associations partly subsidized by government and still others, having no such agencies, are represented by delegates appointed from the tuberculosis control divisions of their public health departments. The Union, however, retains the independent status of a voluntary group with its own constitution and elected officers and issues the transactions of its conferences as the unofficial consensus of scientists from many countries with primary interest in tuberculosis research and control.

The last conference held was at Lisbon in 1937. Unrest in the Iberian Peninsula made travel through Spain undesirable and the delegates gathered at Havre and took ship for Lisbon. This was an agreeable arrangement as it gave time for preliminary discussions, the renewal of old acquaintanceships and the formation of new ones. In Portugal it was decided to hold the 1939 conference in Berlin. The second world war broke out three days before the date scheduled for the meeting. Through the foresight of our State Department no delegates were appointed to represent this country, thus escaping the uncomfortable situation in which those from certain other countries found themselves.

The effect of the war on the International Union was grave but not disastrous. The office was visited by Germans during the years of occupation and while activities were interdicted its library and records were not disturbed. No communication with the outside world was permitted and until 1945 no direct word was received from its Secretary General, Dr. Bezançon, or its executive secretary Dr. Alix Churchill. The last number of the Union's Quarterly Review was issued in January, 1940. This publication, in addition to news and scientific comment, summarized the tuberculosis statistics of the numerous countries holding membership. Access to, or publication of such figures was prohibited during the period of German occupation. This has proved most baffling in any attempt to secure reliable statements on the effect of war conditions on tuberculosis morbidity and mortality, especially in countries which suffered most

from active fighting. It is well known, however, that in areas occupied by the Germans organized public health work languished pitifully. Tuberculosis sanatoria were looted, destroyed or used for other purposes. Patients were discharged with little provision made for their care. In many cases they were put to work. New foci of infection were thus spread through many regions with cynical disregard of patient or community welfare.

After the cessation of hostilities in 1945 immediate interest arose as to the future status of the International Union. The chaos in Europe, difficulties in the matter of transportation and even communication delayed action for more than a year. Furthermore, organization of the United Nations presented a new relationship which required careful thought. It seemed wise to await the result of plans for the World Health Organization which were taking shape under Section IX, Economic and Social Welfare of the United Nations Charter. This was a sound decision since relations have been established with the Interim Committee, under Dr. Chisholm's direction, of most satisfactory promise.

Finally on November 7, 1946, the Executive Committee of the International Union met at its Paris office, 66 Blvd. Saint Michel, at the call of the Secretary General. Representatives were present from Poland, Norway, Belgium, Portugal, England, France and the United States. The last elected President of the Union, Dr. Lopo de Carvalho of Portugal, presided. The Secretary General reported on the difficulties under which the Union had maintained its office during the five years of German occupation. Income from constituent members was wholly lacking. The French Government had made a generous contribution which enabled the continuance of a skeleton staff on reduced salaries. All publication and outside communication was impossible. No material damage had been suffered in the office. Dr. Bezanson then introduced the non-members of the Committee who had been invited to attend, among them Dr. Parisot, liaison officer appointed by Dr. Chisholm, General Secretary of the World Health Organization's Interim Committee.

Dr. de Carvalho welcomed the group and spoke of the persisting need of such an agency as the Union under existing world health conditions. He also confirmed a rumor that the Germans had proceeded with the meeting of the Union called for September, 1939, that with only Axis representatives present new officers had been elected and the Union taken over by the Germans. He told of a visit to Portugal made by a representative of this rump organization who called upon him and attempted to gain his approval of the action taken in Berlin. Dr. de Carvalho flatly refused, stating that he himself would remain in office until his successor was duly elected by a body truly representative of the Union.

Before discussing future plans the United States delegate on the Executive Committee begged leave to introduce the following resolution for the consideration of the members:

"On behalf of the International Union against Tuberculosis, the Executive Committee in formal session at the Headquarters of the Union, 66 Boulevard St-Michel, Paris, November 7, 1946, respectfully presents the following resolu-

tion to the Interim Commission, World Health Organization of the United Nations:

I—*Whereas*, it is recognized that, due to war and post-war conditions, tuberculosis has greatly increased in many regions and threatens to become a world-wide epidemic of serious proportions, and

II—*Whereas*, the International Union against Tuberculosis believes that, to combat this menace to public health throughout the world, the strongest possible organization of national and international resources is essential.

III—*Therefore*, be it resolved that the International Union against Tuberculosis respectfully suggests to the Interim Commission that it give serious consideration to the establishment and maintenance of a strong Division of Tuberculosis within its services, with a competent staff of experts in the Administration of Tuberculosis Control, to promote the development of a coöperative program among Member Nations to combat this disease."

Dr. Parisot, delegated by the World Health Organization (United Nations) to represent it at the Executive Committee of the International Union against Tuberculosis, declared, on behalf of this Organization, that "the latter is willing to establish with the International Union against Tuberculosis a very close collaboration, whether on the scientific plan or (if the Union so wishes) on the administrative plan: for instance, it would place at the disposal of the Union an Office near the seat of the World Health Organization, its staff, its library etc. . . . The Organization wishes to specify that, in proposing this, it does not intend to diminish in any way the autonomy of the International Union against Tuberculosis whose strength is based on its private character and independence, while on the other hand, it considers that a close collaboration between the Executive Committee of the Union and the Secretariate of the World Health Organization would be to their mutual advantage."

After translation, the two documents were unanimously approved by the Committee and the Executive Secretary was directed to acquaint Dr. Chisholm with this action.

The question of when and where the next international conference should be held was then raised. It was pointed out that the Council of the Union had the responsibility of making a decision on these matters. The Secretary General was then empowered to call a meeting of the Council for this purpose. July of 1947 was decided upon as an appropriate time for such a meeting. This will come after the June meeting of the World Health Organization which is expected to come into full existence at that time. We will then be in an advantageous position to clarify more definitely our relations with that body.

The Council will concern itself chiefly with matters of reorganization, the election of officers, suggested amendments to the present constitution of the Union and a discussion of plans for the next conference which will probably take place in some European country during 1948 or 1949. It has been customary for the members to devote a half day to discussion of some scientific topic. Streptomycin was suggested as an appropriate subject for consideration at the forthcoming meeting.

Finally, the Executive Secretary was asked to resume correspondence as soon as possible with all states adherent to the Union reporting the meeting of the Executive Committee and inviting participation on the part of old members in the forthcoming meeting of the Council.

A pleasant interlude in the day's work was a most agreeable luncheon for the Committee Members and guests at the *Cercle Interallié* provided by Dr. Berançon. The club occupies one of the most charming residences on the *Faubourg St. Honoré* with gardens running down toward the *Champs Élysées* and is doubtless familiar to many who may read this account. A number of distinguished French physicians were asked to join us, among them Drs. Poix, Guérin, Édouard Rist and Étienne Bernard. Needless to remark, the food was in the French manner of perfection and the wines of choicest vintage.

The future of the International Union against Tuberculosis under the new political organization of the world will present a number of puzzling problems. The Interim Commission of the World Health Organization has indicated its interest in a strong international voluntary association and expressed its belief that such a non-official agency can be of assistance in a collaborative relationship. This should mean the inclusion, as nearly as possible, of all countries in the membership of the Union.

From the functional point of view it would appear that regional groups might well be established along the lines suggested by the Interim Commission. This would require expansion of the organizational and administrative responsibilities of the central office and would necessitate more liberal financing than in the past.

Again the character of the biennial conferences should receive most careful consideration, having in mind especially social and economic as well as scientific factors which influence the control of tuberculosis. Such questions will come up for consideration at the time of the forthcoming Council meeting and much preliminary thought should be put into the planning of this meeting and preparation of agenda covering essential points for discussion.

PNEUMOPERITONEUM IN THE TREATMENT OF PULMONARY TUBERCULOSIS¹

Results in 710 Cases from 1937 to 1946
ROGER S. MITCHELL,² JOSEPH S. HIATT, JR.,³ PAUL P. MCCAIN,⁴ HERMAN F.

EASOM⁵ AND CHARLES D. THOMAS⁶

Artificial pneumoperitoneum has been used to treat pulmonary tuberculosis at the North Carolina Sanatorium since 1937 and at the Eastern North Carolina Sanatorium since its opening in 1943, with increasing frequency and success. Of the 710 patients who have received pneumoperitoneum at some time during their residence, 474 were so treated for three months or longer; it is upon the latter group, in which pneumoperitoneum has ostensibly been given a sufficient trial, that this report is based. The complications cover the entire 710 cases.

REVIEW OF THE LITERATURE

Since artificial pneumoperitoneum was first used to treat pulmonary tuberculosis by Vадja in 1933 (87), after a suggestion made by Banyai (5) in 1931, to be followed by the latter's persistence since 1934 (6 to 21), so little time has elapsed that comprehensive studies on large series of cases over sufficiently long periods of time have been virtually impossible.

Table 1 is a chronological summary of the reports from all sources which give any results of pneumoperitoneum treatment for pulmonary tuberculosis. Of the 58 reports, 18 cover 5 cases or less and 36 cover 50 cases or less, while 22 reports are based upon a maximum period of observation of one year or less. Recently, however, several reports cover over 100 cases each, for periods of observation of up to four and five years (3, 35, 36, 73). It is of interest that these late reports are favorable, and one is enthusiastic enough to predict that pneumoperitoneum plus diaphragmatic paralysis will mark a greater advance in the treatment of pulmonary tuberculosis than the advent of artificial pneumothorax (36).

Not more than 8 reports can be considered unfavorable to pneumoperitoneum (39, 42, 58, 75, 76, 83, 84, 85). Three of these by one author, Trimble (83, 84, 85), are offset by his most recent, favorable, opinion (86). Of the other 5 unfavorable reports, the largest is a series of 50 cases (42), and the longest maximum period of observation is two years (39). A great many of the papers on pneumoperitoneum, especially those of the pioneer Banyai, unfortunately merely review its history, technique, indications

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TABLE 1

A chronological summary of the literature reporting on the results of the use of pneumoperitonium (PP) as treatment for pulmonary tuberculosis

AUTHOR	NUMBER OF CASES	PROGNOSIS	MAXIMAL PERIOD OF OBSERVATION	PRIOR COLLAPSE		GOOD RESULT	REMARKS
				Phrenic	Any		
1937 Johannides <i>et al.</i> (53)	3	Poor	Short	100%	100%	100%	Recommend phrenic plus PP A preliminary report
Trimble <i>et al.</i> (83)	80	Poor	1 yr.	Most	100%	Some	
Fremmel (45)	8	?	18 mos.	100%	100%	50%	
1938 Trimble (84)	250	Poor	Short	?	?	1.6%	Unfavorable Recommend PP without phrenic Favorable 8 prepared for surgery Small doses; PP has limited use Mid and lower third cavities close more readily than upper third PP relieves tuberculous peritonitis Series of 220 treated for tuberculous enteritis and peritonitis PP relieves digestive symptoms Used mostly for tuberculous peritonitis
Burge (30)	3	Poor	Short	0	0	?	
Hobby (51)	19	?	Short	?	?	Many	
Daniels <i>et al.</i> (37)	21	Poor	1 yr.	100%	100%	72%	
Stokes (80)	41	Poor	2 yrs.	100%	100%	22%	
Bennett (24)	200	Poor	2 yrs.	87%	100%	Many	
Choussat (33)	1	?	9 mos.	?	?	100%	
Banyai (11)	120	?	?	?	?	Many	
Mercador <i>et al.</i> (63)	3	Poor	Short	?	?	Many	
Gomez <i>et al.</i> (46)	Few	Poor	2 yrs.	Most	Many	?	
1939 Brian <i>et al.</i> (26)	3	Poor	1 yr.	100%	100%	100%	Selected cases; never used PP alone Symptomatic improvement only Unfavorable: 20 autopsies 22.5% sputum conversion Effective in selected cases
Bruce (29)	4	Poor	Short	100%	100%	75%	
Trimble <i>et al.</i> (85)	152	Poor	3 yrs.	Most	100%	Few	
Mellics (62)	93	Poor	3½ yrs.	Most	Most	66%	
Centoseudi <i>et al.</i> (32)	30	?	4 yrs.	?	?	Many	
Barnes (22)	1	—	3 mos.	0	?	?	
Hernandez <i>et al.</i> (49)	3	Poor	Short	?	?	66%	
1940 Banyai (20)	30	?	?	?	?	?	Favorable; no figures Right basal lesions least apt to improve with PP
Nunez Bachiller (64)	?	?	2 yrs.	?	?	?	

TABLE 1—Continued

AUTHOR	NUMBER OF CASES	PROG- NOSIS	MAXIMAL PERIOD OBSERVATION	PRIOR COLLAPSE		GOOD RESULT	REMARKS
				Phrenic	Any		
1940—Cont.							
Katz (54)	4	?	5 mos.	?	?	100%	Favorable 21 took PP three months or less Used mostly for abdom- inal tuberculosis Best method for advanced bilateral tuberculosis
Boisliniere <i>et al.</i> (25)	50	Poor	18 mos.	18%	50%	60%	
Adelman (1)	3	?	2 yrs.	100%	100%	100%	
Orsi (66)	5	?	1 yr.	?	?	100%	
McIntyre (60)	11	Poor	2 yrs.	Most	Most	100%	Only 3 sputum conver- sions Opinion changed; PP rec- ommended without phrenic 11% prepared for surgery; hemoptysis controlled in 7 cases PP is technically difficult Results not made clear No cures 5 good results; total not clear
Harrell (48)	12	Poor	9 mos.	9%	100%	25%	
1941							
Brian <i>et al.</i> (27)	15	Poor	2 yrs.	100%	100%	100%	
Dongrey (39)	38	Poor	2 yrs.	?	Most	Many	Unfavorable A few excellent results Very good in exudative tuberculosis
Trimble (86)	300	Poor	7 yrs.	?	Most	Many	
Fowler (44)	56	Fair	3 yrs.	Some	Most	54%	
Rilance <i>et al.</i> (72)	55	Fair	?	100%	100%	35%	
Allen (2)	4	Fair	3 yrs.	50%	100%	Many	A few excellent results Very good in exudative tuberculosis
Lefèvre <i>et al.</i> (56)	5	?	3½ yrs.	Most	Most	?	
Sanchez Acosta <i>et al.</i> (77)	50	?	?	?	?	?	
Hernandez Diaz (50)	5	?	3 yrs.	Most	Most	?	
1942							
Lopez Sendon <i>et al.</i> (58)	26	?	1 yr.	100%	100%	Few	Unfavorable A few excellent results Very good in exudative tuberculosis
Woodford (90)	1	Poor	3 yrs.	100%	100%	100%	
Raimondi (70)	?	Poor	4½ yrs.	?	?	?	
Itturiaga (52)	5	?	?	?	?	?	
1943							
Clifford-Jones <i>et al.</i> (34)	60	Poor	2 yrs.	100%	100%	Some	PP used for short periods only Enteritis made worse by PP Controlled severe hemor- rhage Best in exudative tu- berculosis Used with pneumothorax Old pneumothorax space obliterated in one case
Disney (38)	38	Poor	Short	100%	100%	?	
Keers (55)	1	Poor	3 mos.	100%	100%	100%	
Logie (57)	1	Poor	1 mo.	100%	100%	100%	
Mallick <i>et al.</i> (59)	156	?	1 yr.	?	?	50%	Controlled severe hemor- rhage Best in exudative tu- berculosis Used with pneumothorax Old pneumothorax space obliterated in one case
Tempel (82)	7	Poor	3 yrs.	100%	100%	100%	
McShane (61)	4	Poor	4 yrs.	100%	100%	100%	

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TABLE 1—*Concluded*

AUTHOR	NUM- BER OF CASES	PROG- NOSIS	MAXIMAL PERIOD OBSERVATION	PRIOR COLLAPSE		GOOD RESULT	REMARKS
				Phrenic	Any		
1944 de los Rios (74)	200	?	?	50%	?	80%	Favorable, but vague Used post-partum in a few cases
Stuart (S1)	1	Fair	3 yrs.	100%	100%	100%	
Drury <i>et al.</i> (41)	28	?	Short	76%	?	Most	
Rilance <i>et al.</i> (73)	101	Fair	4 yrs.	50%	50%	50%	
Crow (35)	223	Fair	5 yrs.	Most	Most	44%	
1945 Crow <i>et al.</i> (36)	546	Fair	5 yrs.	100%	100%	60%	Advises PP as a primary procedure Far advanced: 74% im- proved or better; mod- erately advanced: 100% improved or better; 50% sputum conver- sion; used as a primary procedure altogether 10% "success"; 40% "im- proved"
Anderson <i>et al.</i> (3)	110	Fair	4 yrs.	96%	Most	74%	
Edwards <i>et al.</i> (42)	50	Poor	15 mos.		98%	100%	
Schmidt (78)	61	Poor	4 yrs.	Most	Most	?	An X-ray discussion only Favorable
Proton <i>et al.</i> (68)	15	?	Short	Most	?	Many	

and complications, without specific figures on results or follow-up studies. Even Banyai's new text (21) is deficient in this regard.

After eliminating data on the use of pneumoperitoneum in intestinal and peritoneal tuberculosis, it is apparent that, despite the size of the bibliography, there is all too little concrete evidence on which to weigh the effectiveness of the procedure.

Finally, while over 90 per cent of those writing on the subject apparently consider pneumoperitoneum a definitely useful procedure, that it is not so judged by most tuberculosis physicians is a fact made obvious both by wide-spread personal comment and avoidance of the procedure (40).

TECHNIQUE

The technique of administering artificial pneumoperitoneum has been frequently described. Our method has developed along simple lines and has been so safe in many hands over a ten-year period that it is briefly outlined, together with pertinent data on the continuation of treatment.

All injections are given at a site about 2 inches to the left and below the umbilicus. This area is surgically prepared and infiltrated with 1 per cent procaine. A 1-inch, 25-gauge needle is then deeply inserted and infiltration of the peritoneum is carried out. A puncture wound of the skin is made with a sharp needle. Then, for the initial treatment, a 1½-inch, 19-gauge, short-bevel needle is used, in which a small hole has been drilled 1 to 2 mm. from the tip on the long side; this is attached to a 2 cc. hypodermic syringe and penetration through the skin and at least two layers of resistant tissue (pos-

terior rectus sheath and peritoneum) is made with a firm perpendicular twisting pressure. At this point, the syringe is removed and 2 cc. of air are gently pressed into the needle. If this air returns to the syringe easily on drawing back on the plunger several times, the air has presumably been forced into a confined space outside the peritoneal cavity; if the air injected is lost, one may conclude that he is in contact with the peritoneal cavity, and a 1 to 2 mm. further penetration is very carefully made.

The pneumothorax apparatus is then connected with the needle and air is slowly displaced into the needle. If the patient complains of pain at the site of injection when air is given, it is considered that the opening of the needle is not in the peritoneal cavity and further penetration should be made. Mild aching in the shoulders or anterior chest may be noticed, usually some time after administration of air.

Occasionally these tests are inconclusive. Bearing in mind the possibility of penetration of the gut, as in the presence of adhesive peritonitis with a loop of bowel adherent to the inside of the abdominal wall, a new area a few centimeters away is utilized. Rarely, a longer 3-inch "initial" needle will be needed to penetrate thick-walled abdomens. While manometric readings, which incidentally are more positive on inspiration and less positive on expiration, are not always obtainable initially, fluctuations obtained may be of some value in determining the presence of the needle in a free peritoneal space. The initial dose of air varies from 300 cc. to 2,500 cc., depending on the indication: large doses are used to control hemorrhage. The average routine initial dose was 500 cc. and the average second dose was 800 cc.

There is a remarkable variation in the capacity of different abdomens and in tolerance to both the acknowledged early discomfort of pneumoperitoneum and psychogenic factors. This early abdominal and chest pain, aggravated on bending and rolling over in bed, presents a problem not because of its severity, but because, in contradistinction, pneumothorax is relatively painless.

Fluoroscopy in the erect position after the initial dose will usually disclose air under one or both diaphragms and thereby confirm the presence of air in the desired location. Preoperative medication appears unnecessary except in highly nervous patients. Mild postoperative analgesia may be needed for from two days to two weeks, but can often be avoided by judicious reduction in the amount of air and by technical skill in avoiding extraperitoneal administration of air.

The second dose is usually given on the second or third day, the third on the fourth or fifth day, and subsequent doses twice a week, once a week, once in ten days and in some patients, once in two weeks.

The size of refills was also quite variable and ranged from 400 cc. in a small stout person or in one with many peritoneal adhesions, to as much as 3,000 cc. every two weeks in a large multiparous woman with a relaxed abdominal wall. Manometric pressure was seldom carried above plus 8, and often was around plus 5. The average maintenance dose per week in our series of around 40,000 refills was 1,250 cc. in white males, 1,285 cc. in white females, 1,095 cc. in colored males and 1,065 cc. in colored females; or an overall average of 1,165 cc. per week.

As soon as the peritoneal cavity is well distended by refills during three to six weeks or more, the space is entered in one thrust with a plain 1½-inch, 19 gauge, sharp-bevel needle attached to the syringe as before, but without the use of procaine. By this time the administration of pneumoperitoneum is remarkably simple. Abdominal binders are usually tried after a few weeks of treatment and, if well tolerated, are used continuously. We have recently been able to demonstrate by fluoroscopy in a series of patients that a slight further elevation and slight further limitation of

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motion on both quiet and deep respiration of one or both diaphragms may be obtained in many patients with a well-fitted binder. Some seem better able to tolerate pneumoperitoneum wearing the binder, and many are able to space refills out to a longer interval by gradually tightening the binder between them.

A special binder is gradually being evolved for us.⁷ Figure 1 shows a patient wearing the most recent model.

Pneumoperitoneum therapy has been continued in much the same manner as pneumothorax or a course of phrenic nerve crushes, that is, until the disease is well under control or its particular purpose has been accomplished. There is reason to believe that

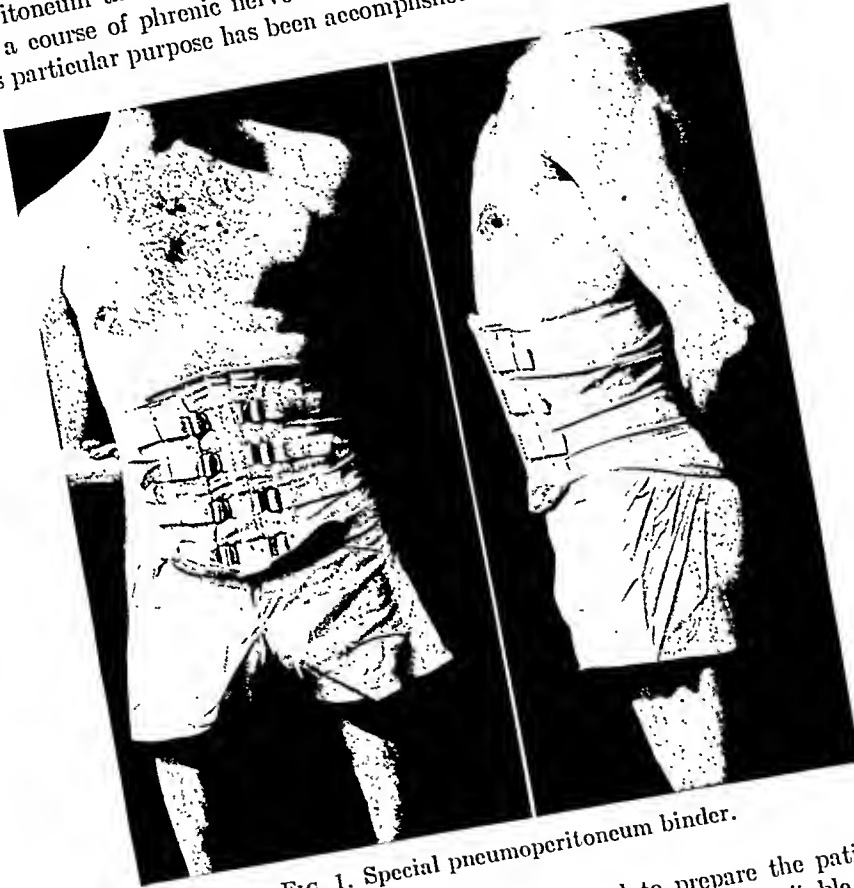


FIG. 1. Special pneumoperitoneum binder.

an effective pneumoperitoneum, when it is not used to prepare the patient for chest surgery, should be continued somewhat longer than pneumothorax (table 5).

Treatment was abandoned for failure to obtain satisfactory diaphragmatic elevation (5 cm. or more), for failure to obtain roentgenological and/or symptomatic benefit, because of certain complications, and, in a few, because of individual unwillingness to tolerate enough air to cause effective diaphragmatic elevation.

⁷ Through the courtesy of Spencer, Incorporated, New Haven, Connecticut, to whom we are indebted.

RESULTS

Table 2 shows the principal form of treatment used in all cases of reinfection pulmonary tuberculosis at the North Carolina Sanatorium for ten years. The distribution of treatment at the Eastern North Carolina Sanatorium was roughly parallel. The chart is divided into colored and white patients and starts one year before the first patient taking pneumoperitoneum was discharged from each division. The increasing use of pneumoperitoneum is apparent; at the time of this report, it had reached a peak at 36 per cent of colored and 25.3 per cent of white patients out of an average census of 710 patients with reinfection type pulmonary tuberculosis at both institutions.

In evaluating pneumoperitoneum, cases falling into the following categories were considered "satisfactory" results:

- (a) All cavities closed by roentgenogram and fluoroscopy, and sputum converted to negative.^s
- (b) "Preparation for chest surgery," which covers reduction in size of cavities on the operated side, closure of cavities on the other side and clearing of infiltration on either side (see example in figure 4).
- (c) "Improved," which includes closure of some but not all cavities, reduction in cavity size, extensive clearing of infiltration, obliteration of an old pneumothorax space, obliteration of a chronic empyema space with or without bronchopleural fistula (figure 6), or definite improvement in symptoms and general condition persisting up to the time of loss of contact or to the date of this report.

No case was classified as "satisfactory" unless the improvement was coincident with a satisfactory diaphragmatic rise after pneumoperitoneum therapy was started. Control of hemoptysis, although "satisfactory," was considered too temporary an effect to evaluate together with factors of a more permanent nature and, therefore, is not included in the figures as a "satisfactory" result.

- (a) "Temporary symptomatic improvement," which includes all those with relief of symptoms and/or roentgenological improvement but with eventual progression of the disease while under pneumoperitoneum treatment.
- (b) No demonstrable benefit, including the serious complications of pneumoperitoneum.

Table 3 summarizes the clinical data of the 474⁹ patients prior to treatment with pneumoperitoneum for three months or longer. It is evident that most of the subjects were poor-risk advanced cases, and that pneumoperitoneum was used principally when pneumothorax was either unsatisfactory or impossible, diaphragmatic paralysis ineffective or inapplicable, or major chest surgery contraindicated or unavailable. Most of the few patients not classified as far advanced were treated in the last two years.

^s Sputum conversion is based throughout this report on twenty-four, forty-eight and seventy-two hour concentrations varying from 2 to 16 in number, and persisting negative through the ambulant stage before discharge.

⁹ 407 at the North Carolina Sanatorium, capacity 600 beds, and 67 at the Eastern North Carolina Sanatorium, capacity 180 beds.

TABLE 2

Distribution of principal forms of therapy for all patients discharged from the North Carolina Sanatorium with reinfection pulmonary tuberculosis from July 1, 1937 to July 1, 1946, plus those resident on July 1, 1946

(Prison Division patients are not included)

YEAR		BED-REST ONLY	PNEUMOTHORAX	PNEUMOTHORAX PLUS PIRENIC	PIRENIC	CHEST SURGERY	PP THREE MONTHS OR MORE	OLEOTHORAX	IN SANATORIUM LESS THAN THREE MONTHS	TOTAL	PP LESS THAN THREE MONTHS
1937-38	W.....	—	—	—	—	—	—	—	—	—	—
	C.....	57	22	3	12	2	0	0	37	133	0
	T.....	—	—	—	—	—	—	—	—	—	—
1938-39	W.....	—	—	—	—	—	—	—	—	—	—
	C.....	57	31	9	22	4	2	0	34	159	4
	T.....	—	—	—	—	—	—	—	—	—	—
1939-40	W.....	69	78	22	57	11	0	0	35	272	0
	C.....	61	41	16	11	6	20	9	36	201	6
	T.....	130	119	38	68	17	20	9	71	473	6
1940-41	W.....	67	49	45	28	16	5	0	33	243	6
	C.....	89	64	24	17	7	21	4	56	284	11
	T.....	156	113	69	45	23	26	4	89	527	17
1941-42	W.....	83	65	30	40	15	7	0	37	277	4
	C.....	90	32	44	12	4	17	1	44	244	9
	T.....	173	97	74	62	19	24	1	81	521	13
1942-43	W.....	80	44	15	39	12	5	0	43	238	5
	C.....	82	32	25	31	8	22	0	38	248	12
	T.....	162	76	40	70	20	27	0	81	486	17
1943-44	W.....	72	39	25	32	15	11	0	37	231	8
	C.....	62	39	31	33	5	15	1	35	221	6
	T.....	134	78	56	65	20	26	1	72	452	14
1944-45	W.....	54	36	25	39	13	7	0	42	216	7
	C.....	63	40	20	40	10	16	0	37	226	15
	T.....	117	76	45	79	23	23	0	79	442	22
1945-46	W.....	44	47	28	55	18	54	0	74	320	20
	C.....	77	27	12	27	4	39	0	68	254	39
	T.....	121	74	40	82	22	92	0	142	574	59
Resident patients July 1, 1946	W.....	56	36	27	25	44	63	0	15	266	32
	C.....	70	34	15	24	11	71	0	15	222	24
	T.....	126	70	42	49	55	134	0	30	488	56
Totals	W.....						165				82
	C.....						242				126
	T.....						407				208

W: white—C: colored—T: total

Note: The first discharge of a patient who had taken pneumoperitoneum was 4-11-39 at the Colored Division, and 7-28-40 at the White Division.

Table 4 subdivides the results of therapy into "satisfactory" and "unsatisfactory," and differentiates the white and colored patients in whom pneumo-

TABLE 3
Summary of pertinent data in 474 cases prior to pneumoperitoneum therapy

	WHITE DIVISION	COLORED DIVISION	TOTAL
Number of cases.....	188	286	474
Sex:			
Male.....	44%	47%	46%
Female.....	56%	53%	54%
Age:			
Range.....	14-69	8-67	8-69
Average.....	35.4	28.2	31.2
NTA classification before treatment:			
Far advanced.....	84%	91%	89%
Moderately advanced.....	16%	9%	11%
Minimal.....	0	0	0
Prognosis:			
Good.....	1%	0.5%	0.4%
Fair.....	24%	15%	18%
Poor.....	62%	66%	65%
Desperate.....	13%	18.5%	16.6%
Sputum positive.....	99%	100%	99.7%
Cavitation:			
Any.....	99.5%	99.2%	99.3%
Multiple.....	Most	Most	Most
Bilateral (approx.).....	50%	75%	65%
Bilateral disease.....	100%	100%	100%
Pneumothorax failure before PP.....	74%	74%	74%
Diaphragmatic paralysis three months or more before PP.....	62%	52%	56%
Pneumothorax and/or diaphragmatic paralysis before PP.....	99%	82%	88%*

* The 12 per cent who had no prior collapse therapy fall almost entirely within the group discharged 1945-46 and the resident patients.

peritoneum was used alone, in combination with a paralyzed diaphragm (figure 3), and in combination with pneumothorax with or without diaphragmatic paralysis.

On the white service the results were consistent and roughly the same whether pneumoperitoneum was combined with other collapse measures or not, the average being 57 per cent "satisfactory."

TABLE 4

Results of pneumoperitoneum therapy at the North Carolina Sanatorium 1937-46, and Eastern North Carolina Sanatorium 1943-46, used alone and in combination with diaphragmatic paralysis and pneumothorax, subdivided into white (W) and colored (C) patients

	WITH DIAPHRAGMATIC PARALYSIS				ALONE: WITHOUT PARALYSIS OF EITHER DIAPHRAGM**		WITH PNEUMOTHORAX		TOTAL	
	With a definitely paralyzed diaphragm		With a possibly paralyzed diaphragm*							
	W	C	W	C	W	C	W	C	W	C
Total treated.....	96	130	7	22	69	128	16	6	188	286
(both W and C).....	226		29		197		22		474	
Satisfactory results										
Cavities closed; sputum negative.....	15	13	2	1	15	14	3	1	35	29
Prepared for chest surgery....	24	22	0	3	9	6	2	1	35	32
Definitely improved.....	19	22	3	2	12	18	4	2	38	44
Total number.....	58	57	5	6	36	38	9	4	108	105
(both W and C).....	115		11		74		13		213	
Total per cent.....	60	44	71	27	52	30	56	67	57	37
(both W and C).....	51		38		37		59		45	
Unsatisfactory results										
Temporary symptomatic improvement.....	15	17	1	6	7	23	3	0	26	46
No improvement or worse....	23	56	1	10	26	67	4	2	54	135
Total number.....	38	73	2	16	33	90	7	2	80	181
(both W and C).....	111		18		123		9		261	
Total per cent.....	40	56	29	73	48	70	44	33	43	63
(both W and C).....	49		62		63		41		55	

* A phrenic operation had been done prior to pneumoperitoneum, but either the status of diaphragmatic paralysis at this time was not clearly stated in the record, or there had been only a partial resumption of function of a previously paralyzed diaphragm.

** A number of these cases had had previous diaphragmatic paralyses, but function had been regained prior to or about coincident with the institution of pneumoperitoneum therapy.

On the colored service results were definitely poorer, being 37 per cent "satisfactory" of the total, and less consistent in that pneumoperitoneum alone was less effective than when combined with diaphragmatic paralysis.

It should be pointed out that no attempt was made to evaluate the relative effect of diaphragmatic paralysis and pneumoperitoneum when both were used; if pneumoperitoneum was used for more than three months, the case was included in this series. The series was not controlled by a preliminary period of

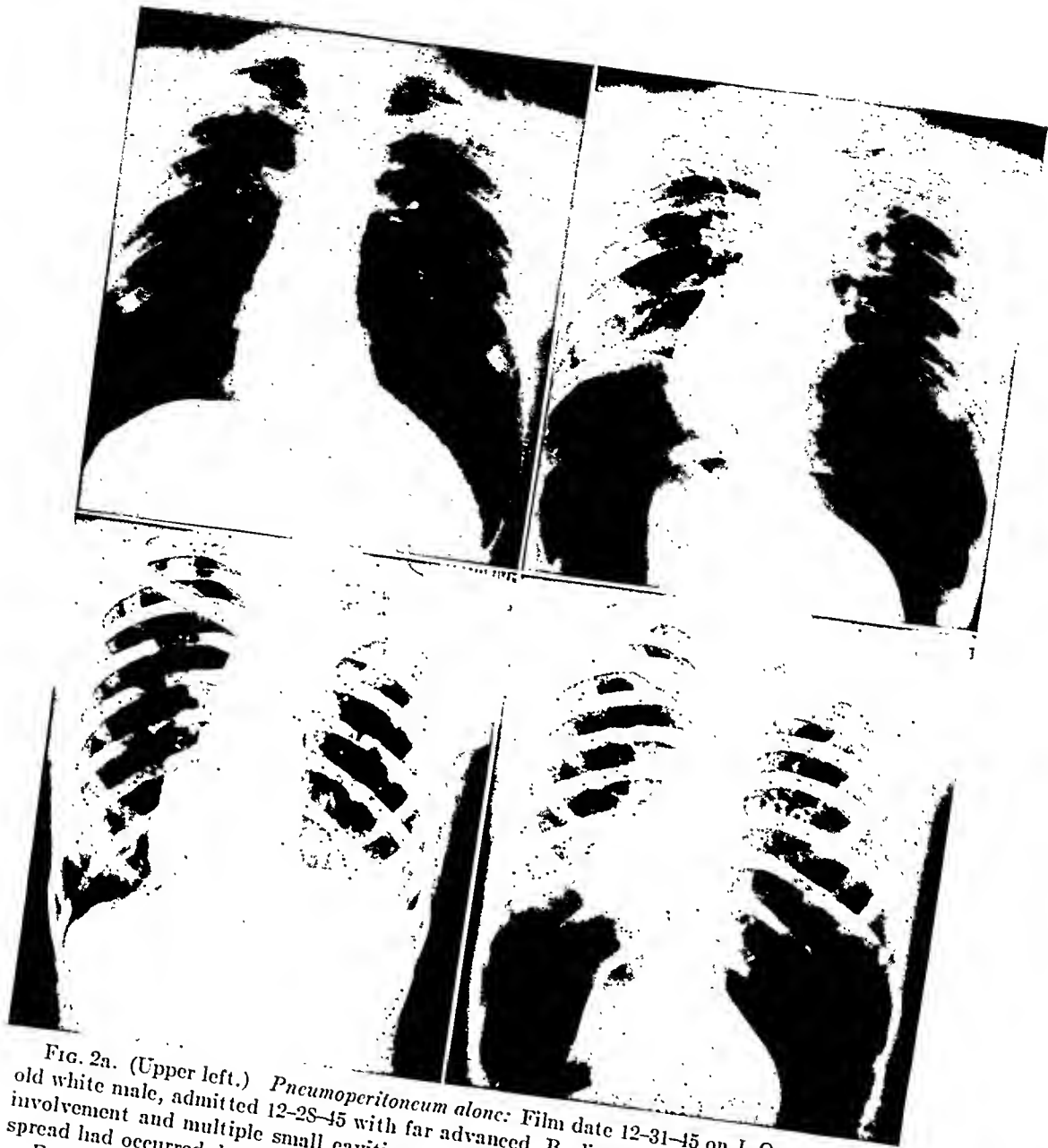


FIG. 2a. (Upper left.) *Pneumoperitoneum alone*: Film date 12-31-45 on J. O., a 27-year-old white male, admitted 12-28-45 with far advanced, B, disease with extensive bilateral involvement and multiple small cavities. Sputum positive on direct smear. Extensive spread had occurred during previous six months.

FIG. 2b. (Upper right.) Film dated 9-28-46 on J. O. shows much clearing and cavity closure from pneumoperitoneum which was instituted 1-12-46; 7 negative seventy-two-hour concentrations since 5-15-46; progressively ambulant since 6-20-46.

FIG. 3a. (Lower left.) *Pneumoperitoneum plus diaphragmatic paralysis*: Film dated 5-12-41 on H. J., a 23-year-old colored female, admitted 5-11-41 with far advanced, C, disease, consisting chiefly in a large cavity in the right upper lobe. Sputum positive on direct smear. Right pneumothorax failed 5-15-41. Pneumoperitoneum was begun 5-22-41; phrenic crush was added on right 6-5-41. Cavity closed and sputum converted to negative in October, 1941.

FIG. 3b. (Lower right.) Film dated 1-23-43 on H. J. shows cavity now closed. Discharged home 2-7-43 after 15 negative sputa. In July, 1946 she was doing house work full-time, feeling well, still taking pneumoperitoneum, lesion stable by roentgenogram and 2 twenty-four-hour concentrations were negative.

bed-rest in most cases, nor by a parallel series on bed-rest. However, all cases in which there was real doubt of there being a "satisfactory" outcome were placed in one of the two "unsatisfactory" categories.

Included among the "improved" patients are 3 instances of successful obliteration of old pneumothorax spaces in which the lung had failed to reexpand after prolonged observation on bed-rest; also included are 5 cases of obliteration of still infected empyema spaces, 2 of which were complicated by bronchopleural fistulae. The use of pneumoperitoneum for this purpose was first reported by Mellies in 1939 (62).

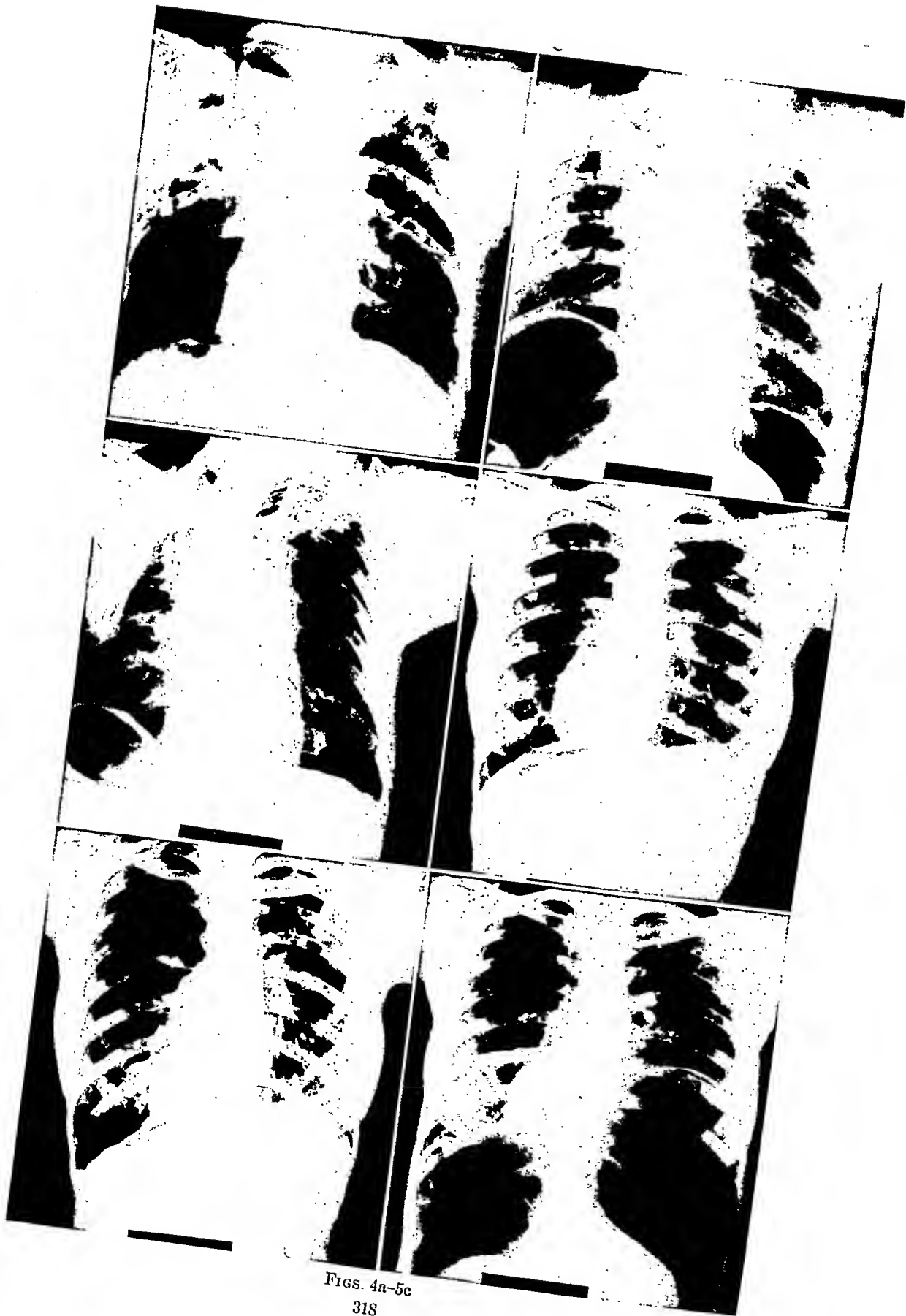
Attention is also called to the 26 white and 46 colored patients who showed temporary symptomatic improvement. Although many of these patients ultimately died or were sent home or to another institution as unimproved, their relief from cough, ease in raising sputum, lowered temperature and feeling of well-being were gratifying, at least for a time. Some so classified were improved roentgenologically and/or clinically for many months only to suffer a relapse. In addition, many of the 236 patients who took pneumoperitoneum for less than three months were afforded symptomatic relief and, at times, control of hemoptysis in their last days, and nearby patients were often spared from listening to severe and prolonged coughing.

The average duration of treatment in the sanatorium among those who took pneumoperitoneum for three months or longer was 51.8 weeks; 54.5 weeks in white patients, and 50.5 weeks in colored.

Follow-up studies revealed that 42 have now received treatment over two years, 14 over three years, 8 over four years and 4 over five years.

The duration of sanatorium plus post-sanatorium pneumoperitoneum treatment of "satisfactory" cases with cavity closure and sputum conversion, not requiring eventual chest surgery, has lasted up to almost six years. Follow-up of all 41 such patients yielded the following information: 21 were alive and apparently well, many working, with cavities still closed according to recent roentgenograms and sputum negative on at least one recent test (routine smear or twenty-four-hour concentration; no gastric specimens, cultures or animal inoculations were used), observed over periods of from four months to four and one-half years following discharge, or an average of eighteen months. In addition to these 21, 3 now require chest surgery after one, three and one-half and four and one-half years, respectively; 2 have reactivated tuberculosis after one and three years; 2 are dead, three and five years after discharge; one died of tuberculosis five years after discharge and three years after stopping pneumoperitoneum in good general condition; one died of tuberculosis four years after discharge despite resumption of pneumoperitoneum. No information is available on 10.

So far only 14 such "satisfactory" cases have discontinued treatment (see table 5). The duration of treatment in these cases varied from 49 to 247 weeks, an average of 133 weeks. Only 8 have been observed over one year after stop-



Figs. 4a-5c
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ping pneumoperitoneum, too few from which to attempt to derive any statistical data.

The duration of treatment in preparation for chest surgery when "satisfactory" results were obtained was from 18 to 239 weeks or an average of 79.4 weeks. Follow-up on all 66 patients classified as "prepared for chest surgery" yielded the following results: 23 were doing well and sputum-negative one month to four years, average twenty months, after surgery; one is now doing well one year after revision of a two-stage thoracoplasty; 13 were still sputum-positive but apparently improved two to fourteen months after surgery; 5 died during or soon after surgery (10 per cent operative mortality); 2 are now respiratory cripples following surgery; 2 had reactivation of disease one and three and one-half years after surgery; no information is available on 3 after successful completion of surgery; one was murdered at home while awaiting surgery; 16 are still awaiting surgery in the hospital.

Eleven of these surgical patients received extrapleural pneumonolysis with packing of methyl methacrylate (Lucite) spheres, an ingenious and apparently successful revival of an old approach to the collapse problem by Wilson and Baker (89). One death occurred in this group.

COMPLICATIONS

The following complications of pneumoperitoneum, used to treat pulmonary tuberculosis, have been reported in the literature. Most articles report serious

FIG. 4a. (Upper left.) *Pneumoperitoneum in preparation for chest surgery:* Film dated 1-21-41 on E. W., a 41-year-old white male, admitted 1-20-41 with far advanced, C, disease; there is heavy excitation and some cavitation on the left, plus heavy active involvement on the right. Sputum positive on direct smear. Left pneumothorax was abandoned 1-28-41 after a "spontaneous" pneumothorax. Left phrenic crush 6-10-41.

FIG. 4b. (Upper right.) Film dated 8-8-43 on E. W. shows much clearing on both sides after pneumoperitoneum was started 1-19-43, but sputum still positive and left apical cavity still open.

FIG. 4c. (Centre left.) Film dated 3-21-46 on E. W. taken just prior to discharge from sanatorium shows end-result of eight-rib two-stage thoracoplasty completed 2-29-45. Pneumoperitoneum was abandoned 1-22-45 just prior to operation. Right negative sputum concentrations since 3-13-45. In July, 1946 he was working four hours per day, 2 sputum concentrations were negative, he was feeling well and lesions were stable by routine postero-anterior and Bucky roentgenograms.

FIG. 5a. (Centre right.) *Pneumoperitoneum plus pneumothorax:* Film dated 3-30-42 on M. K., a 28-year-old white female, readmitted 3-21-42 with far advanced, C, disease with bilateral extensive involvement and sputum positive on direct smear. She had had a right phrenic crush 12-27-39; diaphragmatic function had never been fully regained.

FIG. 5b. (Lower left.) Film dated 5-10-43 on M. K. shows satisfactory left pneumothorax which had been instituted 4-6-42, but disease is now worse on right. Sputum still positive on direct smear. Right pneumothorax failed 5-2-43.

FIG. 5c. (Lower right.) Film dated 1-23-44 on M. K. shows effect of pneumoperitoneum which was started 5-14-43; sputum converted 7-7-43 with great relief of cough and expectoration; discharged to part-time duty as nurse in sanatorium 3-4-45; left pneumothorax stopped January, 1946; pneumoperitoneum stopped 6-10-46 because of febrile reactions after refills. Sputum had been persistently negative on many concentrations; then became positive on 2 occasions without change in stable appearance of roentgenograms and without untoward symptoms. Sputum now negative after modified bed-rest for one month.

peritoneal effusions and peritonitis, aggravation of various types of abdominal hernias, subcutaneous emphysema in various locations, dyspnea and abdominal pain. A number of observers have reported puncturing the gut but there are no reports of serious consequences of this accident. Other less common complications reported are: obliterative adhesive peritonitis (3, 26, 83), acute appendicitis occurring eleven times more frequently than the natural expectancy (73), mediastinal emphysema (16), accidental pneumothorax (16, 72), aggrava-

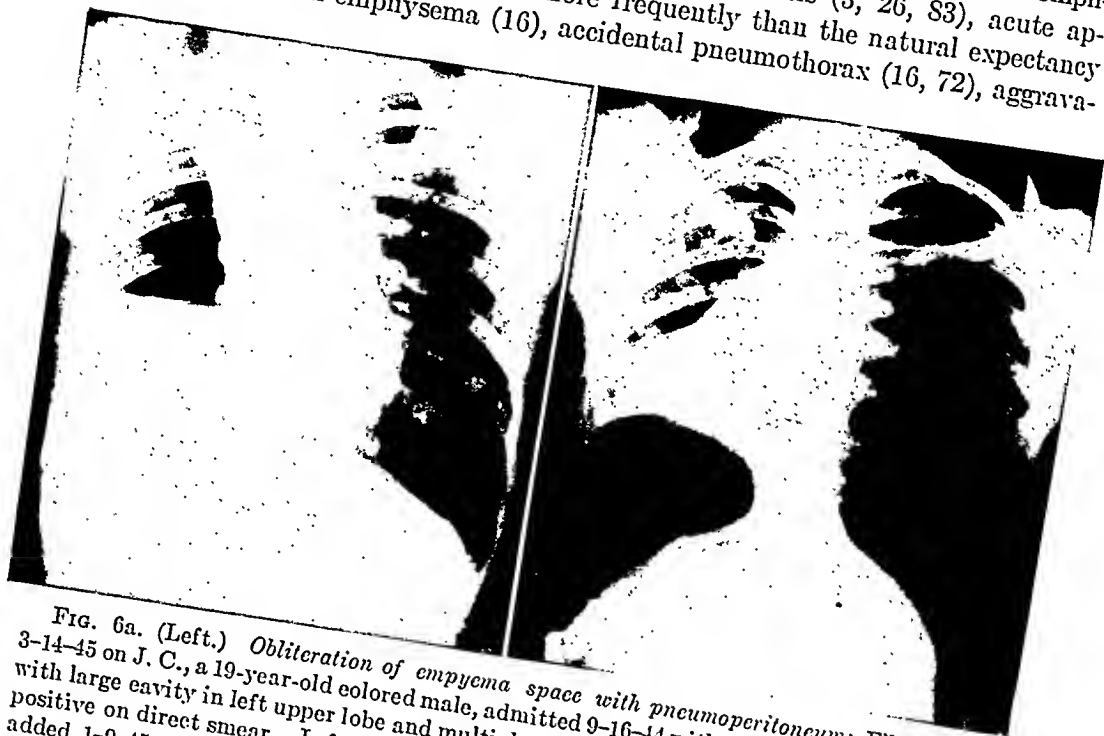


Fig. 6a. (Left.) Obliteration of empyema space with pneumoperitoneum: Film dated 3-14-45 on J. C., a 19-year-old colored male, admitted 9-16-44 with far advanced, C, disease, with large cavity in left upper lobe and multiple small cavities in right upper lobe; sputum positive on direct smear. Left pneumothorax was started 11-15-44 and left phrenic crush added 1-9-45; collapse still unsatisfactory and fluid appeared. Pure tuberculous empyema became apparent in late January, 1946; condition failed to improve on repeated aspirations of thick pus and irrigations for six and one-half months.

Fig. 6b. (Right.) Film dated 5-30-46 on J. C. shows reexpansion of left lung and obliteration of empyema space after pneumoperitoneum was started 8-12-45. The fluid was dried up within three weeks after pneumoperitoneum was started. Right upper lobe cavities no longer visible; now awaiting a left thoracoplasty.

tion of preëxisting heart disease (44), hemoptysis made worse (62), rupture of diaphragm (3), atrophy of diaphragm (62), dysmenorrhea (42, 62), aggravation of preëxisting enteritis (38, 80), hemorrhage from rectum (42), "peritoneal shock" (39), massive atelectasis (26), and lobular atelectasis (62).

Five deaths due to pneumoperitoneum have been reported, 4 due to air embolism (72, 83, 88), and one of sudden death, cause undetermined (48), probably air embolism.¹⁰

¹⁰ Two more cases of fatal air embolism have been reported, one by G. Roche and J. Giron, *Rev. de la tuberc.*, 1944-45, 9, 109, and the other by F. A. H. Simmonds, *Lancet*, April 13, 1946, 250, 530. [Editor]

TABLE 5
Follow-up of all patients discharged with "satisfactory" results with pneumoperitoneum not supplemented by chest surgery who are known to have abandoned pneumoperitoneum, with or without permission

CASE NUMBER	INITIALS	RACE	AGE	SEX	CLASSIFI- CATION BEFORE PP	WITH PNEUMO- THORAX	DURA- TION OF PP IN WEEKS	WEEKS SINCE STOPPING PP	CONDITION DETERMINED MAY-AUGUST, 1946					REMARKS
									X-ray		Recent sputat	Symp- toms	Alive or dead	
									Stable	Un- stable cavity				
1	S. G.	C	28	f	FAC	No	106	56	+		Negative*	0	A	Doing full-time housework PP stopped because of "stroke" Well until March, 1944; no later in- formation Died of pulmonary tuberculosis 10- 10-45; had remained asymptoma- tic over two years after abandon- ing PP Sudden death three years after abandoning PP, cause undeter- mined Working six hours per day Recent loss of 30 lbs.; otherwise well and working; no change by X-ray Working and well Cause of death undetermined Working and well Working part-time for two years; 2 positive sputa four weeks after abandoning PP; now negative Working and well Working four hours per day Working four hours per day; still takes right pneumothorax
2.	L. H.	W	30	f	FAC	No	85	?		Not known	0	D		
3.	M. L.	C	28	f	FAC	No	212	48	+	Negative*	0	?		
4.	A. R.	C	22	f	FAC	No	91	234		+	Positive	+++	D	
5.	S. H.	C	30	f	FAB	No	143	164			Not known		D	
6.	M. H.	C	13	m	MAC	No	101	118	+		Negative*	0	A	
7.	O. O.	C	28	f	FAC	No	174	44	+		2 negative	+	A	
8.	N. J.	W	27	f	MAB	No	122	144	+		6 negative	0	A	
9.	G. L.	W	37	f	FAC	No	178	63			Not known	0	D	
10.	C. H.	W	43	m	FAC	No	126	84	+		Negative*	0	A	
11.	M. K.	W	26	f	FAC	Yes	167	4	+		2 positive	0	A	
12.	W. B.	W	58	m	MAB	No	49	54	+		None	0	A	
13.	E. V.	W	32	m	FAB	No	53	18	+		3 negative	0	A	
14.	T. D.	W	37	m	FAD	Yes	247	8	+		8 negative	0	A	
Averages.....							133	80						

† Sputa are twenty-four to seventy-two-hour concentrations.

* Number of sputa not known in these.

In our 710 cases there was one death directly traceable to pneumoperitoneum, from air embolism following accidental administration of air into the substance of the liver, unquestionably a breach of technique. There were 2 autopsied cases of mixed infection peritonitis, one of which showed a perforated tuberculous ulcer of the ileum, and in neither was there gross postmortem evidence of a puncture wound of the gut.

The complications observed in this series are listed in table 6. In less than 5 per cent did complications lead to abandonment of pneumoperitoneum. None of the "minor" complications were cause for abandonment, except the febrile reactions following refills. These reactions appeared many months after treatment was started and remain unexplained.

Pneumoperitoneum was abandoned because of pain in 46, and dyspnea in 13 patients, two factors not deemed to be true complications. In each instance when pain was the cause of abandonment, it occurred during the first few weeks of therapy.

Unfortunately our records do not show the frequency of intraperitoneal adhesions, but they were observed in varying degree in many cases. Anderson and Winn (3) found them in 71 per cent of patients. In only 5 known cases was it necessary for us to abandon treatment because of such adhesions, usually when the liver and right diaphragm were densely adherent. In one patient, numerous adhesions beneath both diaphragms were severed at laparotomy with subsequent satisfactory diaphragmatic elevation. In one other patient, severance of adhesions was followed by severe shock, apparently due to sudden decompression of the thoracic and abdominal viscera; the patient survived, however, and pneumoperitoneum was continued uneventfully with materially improved diaphragmatic elevation.

Only 3 patients with hernia were unable to continue treatment after applying a well fitted truss.

Needle perforation of the gut during administration of air was suspected clinically on a few occasions, without any serious sequelae.

In one patient a needle, broken during the administration of air, was lost, necessitating a laparotomy to remove it. The patient recovered uneventfully; pneumoperitoneum was not resumed as she came to thoracoplasty a few weeks later.

Peritoneal effusion, clear or cloudy, was observed in a total of 52 patients, or an incidence of 7.3 per cent. Other observers have found the incidence to be 3.8 per cent (44), 8 per cent (36), and 12 per cent (35). Ophuls (65) found that 12 per cent of patients dying of tuberculosis show peritoneal fluid of some degree at autopsy, in the absence of pneumoperitoneum.

Repeated hemoptyses were relieved after removal of pneumoperitoneum in 7 patients.

Acute pleurisy with effusion occurred in 5. The relation, if any, of pleurisy to pneumoperitoneum is not clear, but this incidence seems no more than the natural expectation.

Contrary to the early literature on the subject, improvement in the symptoms

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of tuberculous enteritis was not observed in this series. In fact, the patients with severe enteritis usually did poorly on pneumoperitoneum from the standpoint of their pulmonary disease. Since considerably less air was used in treating enteritis and peritonitis with pneumoperitoneum (5), the degree of visceral

TABLE 6
Complications observed in 710 patients receiving pneumoperitoneum

	NUMBER OF CASES	
	Colored	White
Major complications		
requiring abandonment of pneumoperitoneum in each case		
Serofibrinous peritonitis, tuberculous.....	12	10
Mixed infection peritonitis.....	1	1
Massive ascites.....	2	2
Air embolism, following accidental administration of air into the substance of the liver: immediate death.....	1	0
Incarcerated femoral hernia (pneumoperitoneum resumed later).....	1	0
Spontaneous pneumothorax.....	1	1
Sudden attacks of abdominal pain following refills, possibly due to air embolism.....	1	1
Wheezing cough, relieved after pneumoperitoneum was abandoned.....	0	1
Totals.....	0	1
Frequency of major complications: 4.7 per cent	18	16
Minor complications		
Clear peritoneal transudate, negative on direct smear and culture for acid-fast organisms (therapy not abandoned).....	13	11
Aggravation of hernia:		
inguinal.....	9	2
umbilical.....	7	0
postoperative.....	0	2
Febrile reactions following each refill.....	1	3
Acute appendicitis.....	0	1
Hemoptysis, made less severe or relieved by abandoning pneumoperitoneum.....	6	1
Pleurisy with effusion.....	0	5
Totals.....	36	25
Frequency of minor complications: 8.6 per cent		

compression usually accompanying effectively elevated diaphragms may account for this discrepancy. Clinical enteritis may therefore be considered a contraindication.

Table 7 briefly outlines the pertinent abdominal findings in the 17 autopsies obtained on patients who had received pneumoperitoneum.

Diaphragmatic paralysis following phrenic crush may have a greater tendency

MITCHELL, HIATT, MCCAIN, EASOM AND THOMAS

to fail to regain normal function in the presence of supplementary pneumoperitoneum. Out of the 474 patients taking pneumoperitoneum longer than three months, there were 193 with sufficient elapsed time after operation and sufficient data in the record to survey. Of these, 42 per cent showed complete and 9.5 per cent partial failure to regain normal function in from one to four years after their phrenic crush. Paralysis was considered complete with a 4 or 5 cm.

TABLE 7
Pertinent abdominal findings in all 17 autopsies performed on patients taking pneumoperitoneum: all showed advanced active pulmonary tuberculosis

INITIALS	COLOR	PERTINENT ABDOMINAL FINDINGS	DURATION OF PNEUMOPERITONEUM TREATMENT IN WEEKS
M. D.....	C	Tuberculous adhesive peritonitis with fluid	1
W. R.....	W	No pertinent abdominal findings	2
H. H.....	W	Severe enteritis; small amount of clear fluid	4
L. S.....	C	No pertinent abdominal findings	7
M. D.....	W	Severe mixed infection peritonitis; severe enteritis with a perforated ulcer of ileum	14
G. D.....	C	No pertinent abdominal findings	18
W. M.....	C	Severe tuberculous peritonitis and enteritis	22
W. J.....	W	Massive ascites; severe enteritis; caseous mesenteric adenitis; severe portal cirrhosis; (chronic cor pulmonale)	23
G. C.....	C	No pertinent abdominal findings	24
R. B.....	W	No pertinent abdominal findings	25
G. G.....	C	Mild adhesive peritonitis; no fluid	26
C. G.....	W	No pertinent abdominal findings	27
J. D.....	W	Small amount clear fluid; chronic passive congestion of liver (chronic cor pulmonale, slight); post-surgical death; no abdominal fluid present when pneumoperitoneum was abandoned three months before	28
L. S.....	C	Severe enteritis with perforation of an ulcer of ileum and severe tuberculous peritonitis	33
C. M.....	C	Severe mixed infection peritonitis	39
M. P.....	C	No pertinent abdominal findings	56
J. W.....	W	Severe adhesive tuberculous peritonitis with multiple pockets of cloudy fluid; no enteritis	13

elevation and loss of motion or paradoxical motion of the diaphragm. Paralysis was deemed partial in the presence of elevation plus material reduction in descent of the diaphragm on deep inspiration. No allowance was made for age, nor for the factor of adhesions, but all were initial crushes using a uniform technique of three clamps on the main trunk and severance of all accessory branches found. In a parallel series of 192 initial phrenic crushes, alone and with pneumothorax but without coincident pneumoperitoneum, performed by the same surgeons and controlled in the same manner, 21.3 per cent showed complete and 16.1 per cent partial failure to regain normal function in from one to four years following

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the crush. Although the proof is not as yet available, it is believed that excessive stretching and resultant muscular atrophy, plus supra- and subdiaphragmatic adhesions formed during elevation, both play a part in these findings.

The literature on diaphragmatic paralysis yields almost no specific information on permanent loss of function following phrenic crush. Pinner (67) estimates that at least 10 per cent of supposedly temporary diaphragmatic paralysis become permanent and found the literature uninformative. Crow and Wheelchel (36) observed only 5 per cent permanent paralysis in their 546 patients taking both pneumoperitoneum and phrenic crush; they recommend dissection of the nerve from its sheath and crushing of the nerve only.

COMMENT

These statistical data are not presented as final proof of the efficacy and safety of pneumoperitoneum. It has been frequently, and correctly, stressed that statistics of tuberculosis treatment are profoundly influenced by the convictions of the author, the lack of controls and the pronounced natural tendency of many cases of tuberculosis to improve spontaneously or on bed-rest alone (67). For instance, since pneumoperitoneum may cause discomfort on bending at the waist, the patient is more apt to stay in bed, a fact which one author thought was the principal advantage of pneumoperitoneum (84). The results, however, seem to have been significantly better than those observed on similar advanced cases on bed-rest alone, before the advent of modern pneumothorax and thoracoplasty.

It also may be fallacious to attempt to distinguish between the effects of pneumoperitoneum alone, and in combination with diaphragmatic paralysis, since experience has demonstrated to our satisfaction that each method has its own indications.

Pneumoperitoneum, both with and without diaphragmatic paralysis, provides a simple reversible method of reducing lung volume, uni- or bilaterally, to a variable degree. The amount of useful pulmonary relaxation obtainable there with is unpredictable in the individual case until it has been tried.

It is believed that pneumothorax and primary thoracoplasty should always be considered, before pneumoperitoneum is applied.

However, pneumoperitoneum alone now seems preferable to conventional collapse therapy or simple bed-rest in the case with fairly extensive, bilateral, predominantly productive disease with positive sputum, provided the cavities are not too old or thick-walled (figure 2).

Pneumoperitoneum plus diaphragmatic paralysis is useful in those patients in whom one can be fairly certain of the side from which positive sputum is coming. When the source of positive sputum is not clear after thorough study, pneumoperitoneum alone is recommended for a trial period of from two to six months, since supplementary diaphragmatic paralysis often limits the compression effect of pneumoperitoneum to that side.

Another advantage of applying pneumoperitoneum before diaphragmatic

paralysis is the information gained therewith regarding the mobility and attainable elevation of the diaphragm to be paralyzed (36).

It has been emphasized that pneumoperitoneum may convert an ineffective diaphragmatic paralysis into an effective elevated one. It is believed that pneumoperitoneum may further improve upon diaphragmatic paralysis with a good rise, by abolishing the paradoxical motion thereof (62), which theoretically impairs pulmonary drainage (67).

Pneumoperitoneum has the tremendous advantage over pneumothorax of greater safety and freedom from a variety of serious early and late complications. It has a most practical advantage over pneumothorax and all major forms of surgical collapse in the ease of following the effects of treatment by roentgenograms (36). With almost no exceptions, it may be abandoned and reestablished at will, the space never having been lost to an adhesive peritonitis in our experience.

An "effective pneumothorax" (69) is still unquestionably the most satisfactory collapse measure for pulmonary tuberculosis; but, that it is very limited in its practical application in all those needing collapse therapy cannot be denied. A phrenic crush with good diaphragmatic elevation appears to be amazingly effective at times, in selected cases. Thoracoplasty is now a safe and most dependable procedure in increasing numbers of cases, when they are properly selected and prepared.

However, the vast problem of advanced, particularly bilateral, tuberculosis as seen so frequently in state and county sanatoria remains largely unsolved by these accepted measures.

It is contended that pneumoperitoneum has an important place in the treatment of many of these advanced cases, particularly those with bilateral cavitation, in which pneumothorax is contraindicated, fails or must be abandoned, and major surgery impossible. The practical consideration of the continuing relative unavailability of thoracoplasty in some localities, because of the shortage of facilities, trained personnel and funds must not be overlooked.

CONCLUSIONS

1. In producing a temporary reversible reduction in lung volume, pneumoperitoneum provides an effective measure for the treatment of many cases of advanced pulmonary tuberculosis.
2. Pneumoperitoneum will help prepare many advanced bilateral cases for major chest surgery.
3. In direct contrast to pneumothorax, pneumoperitoneum is a simple safe procedure with only rare serious complications and sequelae, when correctly used.
4. The possibility of using pneumoperitoneum should always be considered in planning the treatment of advanced pulmonary tuberculosis.

SUMMARY

1. The existing literature on pneumoperitoneum is lacking in detailed reports on results of treatment followed over prolonged periods.

PNEUMOPERITONEUM

2. While the vast majority of the literature is favorable, pneumoperitoneum remains in relative disrepute in most quarters.
3. Our observations indicate that pneumoperitoneum is an easy, safe procedure and requires less judgment and experience to apply than pneumothorax.
4. The use of pneumoperitoneum for an average of 54.5 weeks was responsible for 57 per cent satisfactory results in 188 white patients and, used for an average of 50.5 weeks, was responsible for 37 per cent satisfactory results in 286 colored patients with advanced pulmonary tuberculosis, not amenable to conventional forms of collapse therapy.
5. Pneumoperitoneum was useful in relieving symptoms in terminal pulmonary tuberculosis.
6. Pneumoperitoneum was occasionally useful in helping reexpand an "unexpandable" lung and in obliterating empyema space, and in controlling pulmonary hemorrhage, when other methods failed.
7. An abdominal binder is a useful adjunct to pneumoperitoneum in most patients.
8. The complications of pneumoperitoneum given to 710 patients for periods ranging from one dose to 306 weeks were minor in 8.6 per cent, and "major" in 4.7 per cent; pneumoperitoneum was the direct cause of death in one case.
9. Pneumoperitoneum was responsible for a significant increase in the failure of diaphragms to regain normal function following phrenic crush.
10. The presence of tuberculous enteritis was associated with frequent failure of pulmonary tuberculosis to show a satisfactory response to pneumoperitoneum in amounts large enough to cause effective diaphragmatic elevation.

SUMARIO

1. En la literatura relativa al neumoperitoneo no figuran informes pormenorizados acerca de los resultados terapéuticos observados durante períodos prolongados.
2. Aunque la inmensa mayoría de la literatura se muestra favorable, el neumoperitoneo continúa en general en descrédito relativo.
3. Las observaciones de los autores indican que el neumoperitoneo es un procedimiento sencillo e inocuo cuya aplicación exige menos juicio y experiencia que el neumotórax.
4. El empleo del neumoperitoneo durante un período de 54.5 semanas obtuvo 57% de resultados satisfactorios en 188 enfermos blancos, y utilizado durante un promedio de 50.5 semanas, obtuvo 37% de resultados satisfactorios en 286 enfermos de color con tuberculosis pulmonar avanzada que no cedía a las formas habituales de la colapsoterapia.
5. El neumoperitoneo resultó útil para aliviar los síntomas en la tuberculosis pulmonar terminal.
6. El neumoperitoneo resultó, de cuando en cuando, útil para ayudar a reexpandir un pulmón "inexpandible" y para obliterar el espacio empiemático y cohibir la hemorragia pulmonar cuando fracasaban otros métodos.
7. En la mayor parte de los enfermos una faja abdominal resultó un coadyuvante útil del neumoperitoneo.

8. Las complicaciones del neumoperitoneo administrado a 710 enfermos durante períodos que variaron de una dosis a 306 semanas, fueron de menor importancia en 8.6% y de "mayor importancia" en 4.7% siendo la causa directa de la muerte en un caso.
9. El neumoperitoneo fué la causa de un aumento significativo de la capacidad de los diafragmas para recuperar su función normal consecutivamente a la traturación del frénico.
10. La enteritis tuberculosa fué aparentemente una contraindicación del empleo del neumoperitoneo a dosis suficientes para el tratamiento eficaz de la tuberculosis pulmonar.

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TRANSVERSE MYELITIS ACCOMPANYING TUBERCULOUS MENINGITIS^{1,2}

R. H. RIGDON

Tuberculous infection of the brain, spinal cord and their coverings is a common pathological process. The clinical manifestations in such cases indicate frequent involvement of the brain and its meninges when compared to that of the spinal cord and its meninges. This variation may be explained by the difference in quantity of tissue rather than by either specific affinity of the tissue for this bacterium and its toxin, or on any anatomical bases.

Tuberculous involvement of the spinal cord in this instance may be considered to be either a metastatic lesion or the result of a direction extension of the infection from adjacent tissues. Toxins from this organism at one time were considered to be significant in the production of necrosis of the spinal cord (1). Rich (2) in discussing tuberculous meningitis says, "the entire appearance is that of a severe hypersensitive reaction, with marked inflammation and necrosis. The infection not infrequently extends along the blood vessels into the superficial layer of the cortex. In addition, small superficial infarctions of the cortex may result from occlusion of infected vessels. The symptoms of tuberculous meningitis appear to be due principally to five effects upon the central nervous system: (1) Mechanical irritation, (2) hypersensitivity, (3) vascular obstruction, (4) extension of infection to the nervous system, (5) increased intracranial pressure."

Solitary tubercles may occur in the spinal cord with or without meningitis. Kupka and Olsen (3) found 87 cases reported in the literature and added one. When a tuberculoma is accompanied by meningitis the clinical manifestations may be both that of a tumor and that of an infection.

The mechanism of the effects produced by Pott's disease on the spinal cord is not obvious in all cases. The cord may be traumatized directly by the collapse of a disintegrating vertebra. An extradural or subdural abscess may be associated with the diseased vertebra and exert pressure on the cord. Cadwalader (4), in an article on paralysis in Pott's disease, reviewed the earlier literature and discussed the problem both from a clinical and pathological standpoint. He said, "I have been able to find only two cases described in which paralysis developed instantaneously without deformity of the vertebrae." In reviewing this problem, Cadwalader cites Kraske who observed pressure on the cord in 6 of 58 cases of Pott's disease. Fischler (5) in 20 cases found compression of the cord produced by a dislocated vertebra in 9 per cent of the cases, by an abscess in 17 per cent, while *pachymeningitis externa* was responsible for 74 per cent of the

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cases. Cadwalader emphasized in his cases of Pott's disease that necrosis of the spinal cord may result from the vascular obstruction that may accompany a tuberculous reaction.

Harbitz (1) observed a woman, aged 25 years, who first complained of coryza, cough, fever, headache and pain in the back. A little later the neck became stiff and it became more and more difficult for her to turn in bed, her legs becoming paretic. The abdominal reflexes below the umbilicus disappeared and there was some hyperesthesia in the lower extremities. The fever continued, the lower extremities became completely paralyzed and irregular contractions appeared in the right arm and right half of the face. A lumbar puncture showed 1,100 cells per cubic millimeter, a majority of which were lymphocytes. The patient died one month after the onset of the symptoms. There was a diffuse meningomyelitis involving the whole cord. Harbitz said, "there may be doubt as to whether the symptoms depended on the changes in the cord itself or in the nerve roots and spinal ganglions; but it seems reasonable to assume that the changes in the membrane and the roots therein were the most important at the time as the changes in the cord itself, and with the marked edema, must have resulted in great functional disturbances. The edema may have been caused partly as the result of the inflammatory changes in the veins and resulting stasis, but it may also have been produced by toxic action from the great number of tubercles in the membranes."

Keschner and Davison (6) reported a case of a woman, aged 30 years, who developed lancinating pains in the right thigh and weakness in the right lower extremity. Neurological examination showed weakness of the left upper and right lower extremities which was most marked in the extensions of the foot. The deep reflexes were hyperactive, more so in the right lower extremity. There was a right Babinski sign. Sensory examination revealed hyperesthesia, hypalgesia and hypothermesthesia below the fourth dorsal dermatome, except in the perianal region in which sensation was normal. The spinal fluid contained 7 cells per cubic millimeter and a total protein of 41.5 mg. per cent. She had extensive pulmonary tuberculosis. Death occurred approximately one year following the development of pains in the thigh. The spinal cord showed extensive necrosis between the first and sixth thoracic segments. There was an accumulation of an inflammatory exudate in the subarachnoid space about the cord. The blood vessels of the meninges were thickened and their walls were infiltrated by inflammatory cells. The lumina of some of the vessels were obstructed. Keschner and Davison (6) said, "the spinal cord was subjected to two types of changes: (1) perivascular infiltrations, thickened adventitial coats and compression of the vessels and cord by the abscess, leading to vascular obstruction; (2) a direct invasion of the spinal cord at its margins by the inflammatory process. The latter process was less extensive than the former."

Recently 2 cases of generalized tuberculosis with extensive necrosis of the spinal cord were studied in this laboratory. The significant clinical and pathological findings are as follows:

CASE REPORTS

Case 1: The patient was a colored woman, aged 21 years, who was delirious when brought to the hospital. Her husband stated that she was in good health until ten days previously, at which time she first complained of severe frontal headaches, general malaise, fatigue and a feverish sensation. There were vague pains and a feeling of tingling in the lower extremities. Her feet and legs were completely paralyzed five days before admission and two days later she lost control of the anal sphincter and had to be catheterized.

On admission her temperature was 103° F.; pulse 110; respiration 24; the blood pressure, systolic 125 and diastolic 75. She was completely disoriented. The neck was stiff and its flexion caused pain. There was a flaccid paralysis of both lower extremities. The muscles of the abdomen and thorax were also paralyzed. Sensation was absent below the level of the second intercostal space anteriorly and the level of the spines of the scapulas, posteriorly. There was some disturbance in sensation along the lateral surface of the right arm and forearm. The right patellar reflex was absent, the biceps, triceps, ulnar, radial and left patellar reflexes were active. Both upper and lower abdominal reflexes were absent. There was no Babinski or ankle clonus.

The cerebrospinal fluid showed 318 cells, of which 81 per cent were polymorphonuclear leucocytes and 19 per cent lymphocytes. The sugar was 31 mg. per cent and the total proteins were 295 mg. per cent. Acid-fast bacilli were cultured from this fluid. A cerebrospinal fluid Wassermann test was positive. The patient's condition declined rapidly and she died twelve hours following admission.

Necropsy findings: Postmortem examination was made five hours following death. The body was that of a poorly nourished, colored female about 20 years of age. The peritoneum was covered with numerous small tubercles and there was a small amount of yellow fluid within the abdominal cavity. Fibrinous and fibrous peritoneal adhesions were present. A similar tuberculous process was present on the right and left sides of the thoracic cavity. The mediastinal lymph nodes showed extensive caseation. Numerous small tubercles were present in the lungs. Most of them were less than 0.5 cm. in diameter. There were no cavities in the lungs. Microscopically the tuberculous lesions showed both the exudative and proliferative types of reaction. Similar tuberculous lesions were present in the liver and spleen. No acid-fast bacilli were found in these tissues.

The brain weighed 1,437 g. Its superior surface was hyperemic and covered by a slightly cloudy exudate. A thick purulent exudate covered the base of the brain. No changes were observed in multiple gross sections through the brain. The spinal cord, with its membranes, was removed from the cervical level downward. A thick purulent exudate covered the entire surface of the cord. It was thicker over the lumbar portion than over the cervical. Many sections were made through the cord. A focal area of necrosis 0.5 to 1.0 cm. in diameter was present in the upper portion of the thoracic cord. It was impossible in this area to recognize the gray and white tissue; however, anatomical structures could be recognized in the greater part of the cord. Smaller foci of necrosis were noted in different portions of the cord.

Histological observations on central nervous system tissue: Numerous foci of acute degeneration were present in both the gray and white matter of the cord. An irregular zone of necrosis was frequently found at the periphery (figure 1). The inflammatory exudate followed some of the blood vessels into the cord. No giant cells or areas of caseation were observed within the substance of the cord. The subarachnoid space was diffusely infiltrated with both mononuclear cells and polymorphonuclear leucocytes (figure

2A). An occasional giant cell was present. In the thoracic portion the dura mater was the site of a tuberculous reaction characterized by a localized area of caseation and epithelioid and giant cells. It is suggested that this may have been the site of an extradural abscess which extended inward to involve the cord. The nerve roots within the subarachnoid space were surrounded by the exudate and some were infiltrated with mononuclear cells (figure 2B). Groups of the nerve fibres were degenerated in many of these nerves (figure 3B). The wall of essentially every blood vessel was infiltrated with this exudate and their lumina were occluded by recent thrombi (figure 3A).

The meninges covering the brain exhibited changes similar to those about the spinal cord. Acid-fast bacilli were cultured from the spinal fluid.



FIG. 1. A portion of the periphery of the spinal cord showing the extensive degeneration of the myelin sheaths. A similar focal degeneration frequently occurred within the substance of the cord. Formol-thionin, myelin sheath stain.

Case 2: The patient was a colored male, 23 years of age, who said he had been in good health until three weeks before admission to the hospital. He was picking cotton when he suddenly became weak, developed a headache and had a severe pain in the epigastric region which radiated around to the back. He remained in bed following the onset of his illness. The headache persisted and there were attacks of nausea and vomiting. The patient thought he had fever. Approximately ten days following onset the patient noticed that he was unable to move his legs and that there was pain "under his knees and in the hips" when his lower extremities were moved. Two days before admission he was unable to void and the following day was catheterized.

On admission, five days preceding the time of death, the temperature was 103° F.; pulse 112; respiration 24; the systolic blood pressure was 120 and the diastolic was 80 mm. of mercury. He was acutely ill but cooperated satisfactorily during the examination. His weight was 130 pounds; this was 26 pounds less than his normal weight. There was

tenderness in the costovertebral area, bilaterally. There was a flaccid paralysis of both lower extremities. The cremasteric, lower abdominal and patellar reflexes were absent.

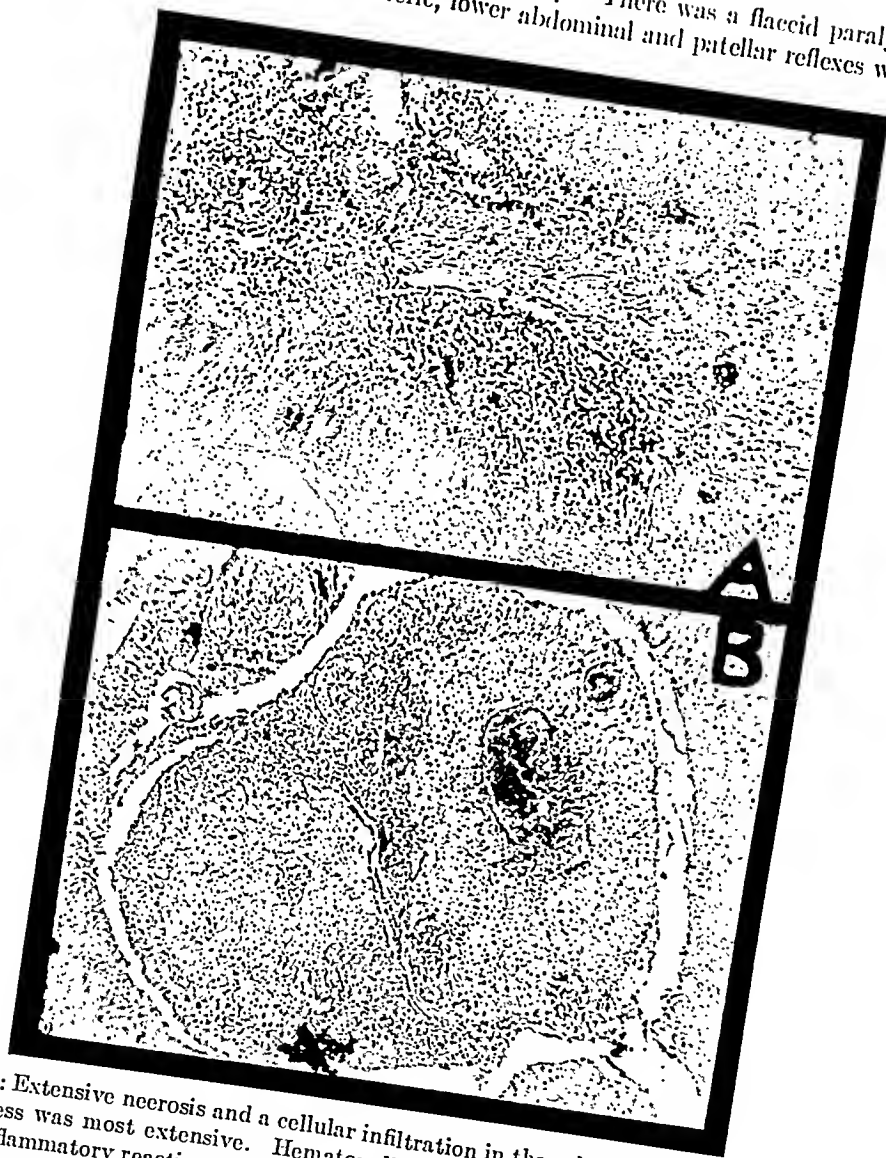


FIG. 2. A: Extensive necrosis and a cellular infiltration in the subarachnoid space. The former process was most extensive. Hematoxylin-eosin stain.
 B: The inflammatory reaction surrounded and extended into many of the spinal nerves. Note the collection of mononuclear cells about the vessels in this nerve. Hematoxylin-eosin stain.

Ankle clonus, Kernig and Brudzinski reflexes were present. There was good tonus of the anal sphincter. The pupils reacted to light and accommodation. The cerebrospinal fluid showed 186 cells, of which 78 per cent were lymphocytes and 22 per cent were polymorphonuclear leucocytes. The protein was more than 1,000 mg. per cent. The sugar was 26 and 48 mg. per cent on two occasions. Chlorides were 470

mg. per cent. Cultures were negative. The serological reactions were negative on both the blood and the spinal fluid.

The patient gradually became lethargic, then semicomatose and died five days following admission to the hospital.

Necropsy findings: The postmortem examination was made forty-eight hours following death. The body was that of a well developed and fairly well nourished young colored adult male. The serous cavities were free of fluid; however, there were extensive fibrous adhesions binding both lungs to the parietal pleura. The lungs were congested, especially in the posterior half. Small tubercles were present in the lower right lobe and on the pleural surface of this lung. No cavities were present. Several small tubercles were present in the spleen and liver. Microscopically more tubercles were found in the lungs

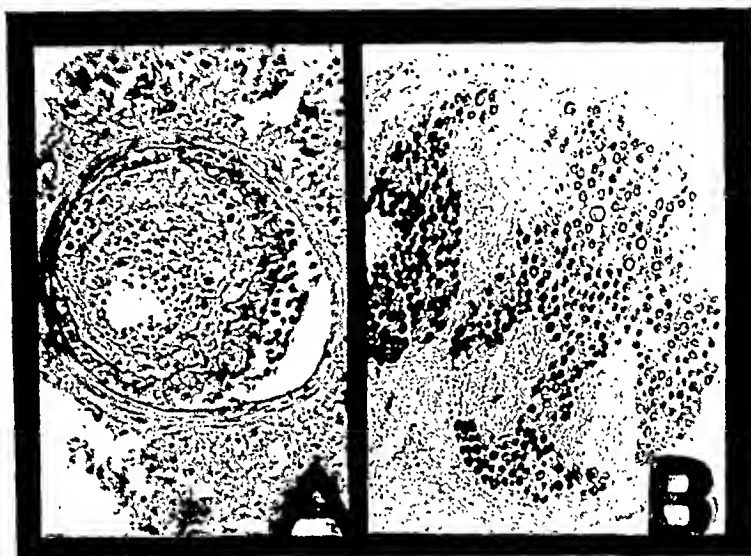


FIG. 3. A: The lumen of essentially every vessel about this spinal cord was occluded by recent thrombi. Sometimes the walls of those vessels were infiltrated by the inflammatory reaction. This shows one of the occluded vessels. Hematoxylin-eosin stain.

B: Extensive degeneration of the myelin sheaths was present in many of the spinal nerves. This shows an absence of myelin sheaths in focal areas within this nerve. Some of the remaining sheaths failed to stain as deep as the normal. Formol-thionin myelin sheath stain.

than were suspected from the gross examination. Tubercles were also found in the adrenals, lymph nodes and prostate. The tubercles in all the viscera were primarily of the proliferative type.

The urinary bladder contained approximately 1,500 cc. of urine. The bladder reached the level of the umbilicus.

The brain weighed 1,390 g. There was a gelatinous exudate over the base of the brain. A few tubercles were present along the lateral sides of the cerebral hemispheres. No pathological changes were observed in multiple sections through the brain except for many tubercles along the walls of the ventricles. The entire spinal cord was swollen and covered with a thick, gelatinous exudate. In the upper lumbar region of the cord there was a local area of enlargement which involved 1.5 cm. Approximately 4 cm. above this area

of swelling was one which involved 1.0 cm. of the cord. When the spinal cord was sectioned it was difficult to outline the gray and white matter in these two areas of enlargement. No definite tuberculoma was found within the cord.

Histological observations on central nervous system tissue: The lesions in the spinal cord were identical with those described in case 1. There were more lymphocytes in the inflammatory reaction in this than in the previous case. In one section there was a collection of tubercles between the pia and arachnoid in which there were several giant cells and epithelioid cells. The reaction here was very conspicuous in contrast to that elsewhere about the central nervous system. The tuberculous reaction was extensive about the base of the brain and in many sections the portion of the cortex adjacent to the surface was necrotic. A perivascular reaction accompanied many of the vessels as they extended down into the brain substance. Acid-fast organisms were demonstrated about the spinal cord.

DISCUSSION

It is obvious from the 2 case reports that both patients had a most extensive and wide-spread tuberculous involvement throughout their bodies. The transverse myelitis resulted from extensive necrosis which occurred in the upper thoracic region of the spinal cord in one and in the lumbar region in the second case. These areas of necrosis and the other focal areas of degeneration within the cord apparently resulted from the occlusions affecting the vessels in the subarachnoid space. The variation in the extent of the necrosis in the different segments of the cord, the involvement of both the white and gray substance, the absence of a specific tuberculous reaction within the cord and the location of a necrotic zone at the periphery of the white substance all may be explained adequately by the thrombotic occlusions of vessels surrounding the cord.

The greater part of the inflammatory reaction in the meninges in these cases is similar to that described by Rich (2) in hypersensitive individuals. Vascular occlusions are characteristic lesions in this type of tuberculous reaction. One might consider this necrosis in the cord to be the direct result of the effect of tuberculous proteins on the medullary sheaths; however, in the absence of tubercles within the cord this appears to be unlikely. Furthermore, the pia mater is not always destroyed, even over those areas of necrosis within the cord, such as might be expected if the degeneration in the cord were the direct result of the tuberculous reaction in the subarachnoid space. If this necrosis in the cord were a part of a hypersensitive reaction it would seem that it would occur more frequently in cases of generalized tuberculosis.

The failure to observe any tuberculoma in the cord and any tuberculous involvement of the vertebrae apparently would eliminate primary mechanical pressure. Furthermore, the areas of necrosis were multiple and varied in size and location within the cord. A tuberculoma was not demonstrated within the central nervous system of these cases, such as Rich and McCordock (7) have described. The examination of this tissue, however, was not as minute as that by these investigators.

Focal areas of necrosis in the spinal cord have been observed by others in tuberculous meningitis in which occluded vessels were present (1, 4, 6). Cases

of softening of the cord with metastatic tumors have been reported (8, 9, 10). In these cases the tumor masses produced obstruction to the circulation to cause the necrosis. Chung (11) points out that syphilitic thrombosis of the vessels of the cord is a most important single factor in causing the sudden onset of paraplegia. Keschner and Davidson (6) consider that atherosclerosis and syphilis are the two most common causes of vascular occlusions in the spinal cord; of these, syphilis is by far the most common. The pathological changes in the cord due to sclerosis of the spinal vessels are much less frequent than those in the brain due to disease of the cerebral vessels. Mackay (12) in 1939 discussed the problem of vascular occlusion and necrosis of the spinal cord in cases of chronic meningitis. Jaffe and Freeman (13) in 1943 published a review of spinal cord necrosis and softening of obscure origin.

The sudden onset of paralysis in necrosis of the spinal cord is interesting. Cadwalader (4) says that "no variation in the character of the development of spinal paraplegia could be more striking than is the onset of paralysis in acute softening of the spinal cord caused by obliteration of the spinal vessels." One of the cases reported by Greenfield and Turner (14) was characterized by a sudden onset of paralysis. A case of necrosis of the cord reported by Spiller (8) likewise had a sudden onset of clinical symptoms. The first patient reported in this study observed pain and tingling in the lower extremities ten days preceding death, and the lower extremities were completely paralyzed only five days before death. The second case observed weakness in the lower extremities and then paralysis approximately ten days following the onset of his illness.

It is seldom that one encounters 2 cases as similar as these. They were both colored, one a female, aged 21 years, and the other a male, aged 23 years. Both patients were considered to be well until the onset of illness, ten and thirty days previous to death. The onset of paralysis was sudden and involved the lower extremities. Both patients lost control of their urinary bladders, while one also lost control of the anal sphincter. Both cases had a wide distribution of tubercles throughout the viscera of the body. There were no cavities in the lungs of either. The histological reactions about the tubercles likewise were similar; in fact, the sections were so much alike that one case could be substituted for the other without anyone observing any significant difference.

SUMMARY

Two cases of transverse myelitis are reported in young colored adults who had generalized tuberculosis and tuberculous meningitis. The acute paralysis resulted from necrosis of the spinal cord produced by vascular occlusions resulting from the tuberculous reaction in the meninges and wall of the blood vessels about the cord.

Spinal-cord necrosis secondary to vascular occlusions has been observed frequently; however, this process occurring with tuberculous meningitis apparently is infrequent.

A vascular occlusion should be suspected in any case in which there is a sudden onset of paralysis.

SUMARIO

Comunicanse dos casos de mielitis transversa en jóvenes de color que padecían de granulía y meningitis tuberculosa. La parálisis aguda provenía de la necrosis de la médula espinal producida por oclusiones vasculares debidas a la reacción tuberculosa en las meninges y pared de los vasos sanguíneos perimedulares. La necrosis de la médula raquídea secundaria a oclusiones vasculares ha sido observada frecuentemente, pero, aparentemente rara vez en conjunción con la meningitis tuberculosa.

Debe sospecharse oclusión vascular en todo caso en que se presente súbitamente parálisis.

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MANAGEMENT OF PRIMARY TUBERCULOSIS IN CHILDREN^{1,2}

R. V. PLATOU

Your very presence here indicates your appreciation of and interest in programs for the control of tuberculosis, of which recognition and management of childhood forms play so important a part. Routine skin testing or roentgenological examination of children has been integral in most such programs. Physicians are increasingly cognizant of the simplicity, usefulness and objectives of these surveys. Simply because lesions of primary infection are admittedly impossible to demonstrate during life in the majority of cases, tuberculin testing has been and will undoubtedly continue to be the most satisfactory method for case-finding in children; modern improvements in technique have removed almost all vestiges of its objectionable features.

There is surprising lack of unanimity of medical opinion regarding management of positive reactors. Whereas all agree that a positive tuberculin test gives no valid information regarding type, activity, infectivity, duration or source of infection, altogether too many physicians are content to note merely that a child does not appear to be ill, that roentgenograms show either a typical primary complex or no lesion, and that a social worker or public health nurse is arranging for the conventional roentgenological study of environmental contacts. Though such complacency may be warranted for the majority of children who react to tuberculin, numerous exceptions in our own experience at Charity Hospital in New Orleans have caused real concern over this all too prevalent attitude.

Honored by an invitation to discuss management of primary tuberculosis in children, I undertook an analysis of all deaths from tuberculosis which occurred in our hospital during the last ten years. This analysis only served to aggravate my own chronic concern over oft-neglected aspects of management. These fresh data only add more weight to familiar contentions, but are entirely pertinent for brief review here. Nothing in this study lessened our respect for potential dangers of this ordinarily benign phase of tuberculosis. Even if effective means for eradication of tubercle bacilli were available, the ounce of prevention would still be worth more than the pound of cure.

From July, 1936 through June, 1946 there were 153 deaths among 784 recognized clinical cases of tuberculosis occurring in over 82,000 children admitted (table 1). In this same period there were 28,544 deaths from all causes, almost 8 per cent of which were in children. Tuberculosis accounted for 9.8 per cent of the total deaths, and it was startling to find that it was responsible for over 6 per cent of all deaths in children.

The distribution by age of these deaths from tuberculosis in children was compared with that occurring in the United States (1) and in the State of Louisiana

¹ From the Department of Pediatrics, Tulane University School of Medicine, and Charity Hospital of Louisiana at New Orleans, Louisiana.

² Condensation of an address presented before the Southern Tuberculosis Conference at Jacksonville, Florida, October 3, 1946.

(2) in 1944; the similarity of resultant curves (chart 1) was of course expected, with deviation toward a lower percentage of deaths in the older age group of our patients explainable by the fact that this study included children to age 12 only. The mean duration of terminal illness appeared to be shorter by all four criteria than we had anticipated (table 2). When contact was known, it always antedated symptoms by months or years. The first symptoms which could even retrospectively be attributed to tuberculosis were ordinarily mild and rarely led to medical examination until weeks or months had passed. Definite symptoms

TABLE 1
Tuberculosis in children—Charity Hospital, New Orleans
Ten-year period ending June 30, 1946

	TOTAL	CHILDREN	
		Number	Per cent
<i>Admissions, all diseases</i>			
White.....	247,085	40,872	16.5
Colored.....	279,863	41,565	14.9
Total.....	524,948	82,439	15.7
<i>Admissions, tuberculosis</i>			
White.....	4,540	268	5.9
Colored.....	3,620	516	14.2
Total.....	8,160	784	9.6
<i>Deaths from all causes</i>			
White.....	12,960	880	6.8
Colored.....	15,584	1,371	8.82
Total.....	28,544*	2,251**	7.90
<i>Deaths from tuberculosis</i>			
White.....	1,288	36	2.79
Colored.....	1,525	117	7.67
Total.....	2,813*	153**	5.45

* 9.8 per cent of all deaths were due to tuberculosis.

** 6.1 per cent of all deaths in children were due to tuberculosis.

characterizing the terminal episode had usually been present for about three weeks before medical examination and hospitalization. A strongly presumptive diagnosis of tuberculosis was justified in most patients at this time, and over 80 per cent of the children had expired within three weeks of admission. The symptomatology of fatal forms of tuberculosis in children is well known and perhaps remarkable only for its monotonous and ominous similarity. The three most prominent symptoms for each patient were tabulated as they occurred chronologically. Table 2 contributes no great surprises, but it does reveal that even the commonest and most diagnostic features may be obscure, secondary in importance or late in appearance. The significant lesions accompanying these symptoms discovered by clinical and roentgenographic means and confirmed by

necropsy in over half the cases consisted of phthisis in 58, meningeal in 50 and miliary involvement in 41; besides these three predominant lesions, 21 others were described, making a total of 170 discernible tuberculous lesions among these 95 patients. The term phthisis was used here in the broadest sense, to include a wide variety of pulmonary consolidations, many indistinguishable during life from nontuberculous lesions. It is noteworthy that nontuberculous complications were encountered in the terminal illness of only 18 patients.

One hundred and fourteen of these 153 deaths occurred before the fifth year; chart 2 confirms the experiences of others regarding distribution of deaths during these early years. During the first year, most deaths occurred between the third

Tuberculous Deaths in Children - Distribution by Age -

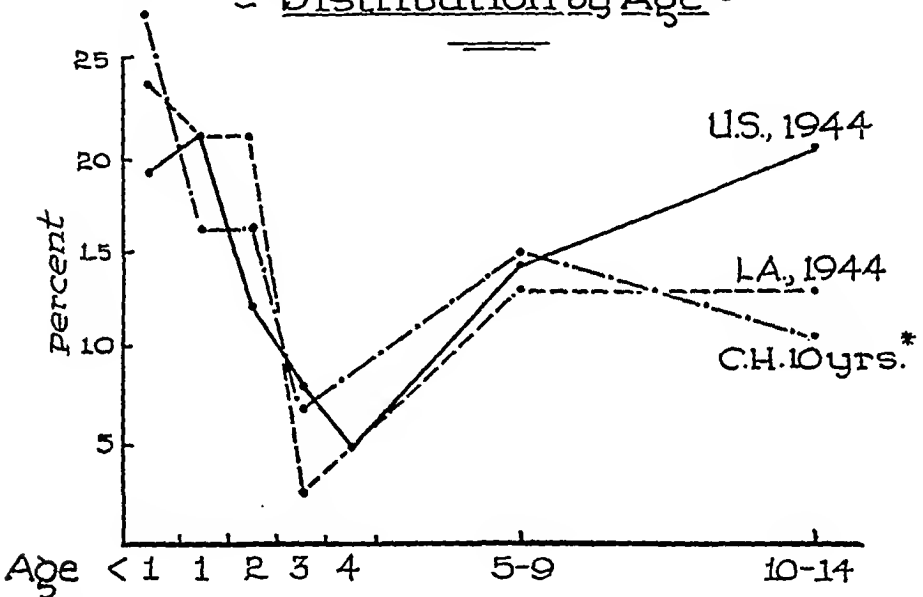


CHART 1

and ninth months. It seems reasonable to explain these curves by more intimate and continuous exposure of infants and toddlers rather than to invoke somewhat nebulous concepts of immunological immaturity.

The source of infection was known for only 26 of these patients and strongly suspected for 11 others. Among these 37, contacts were known to be with a single source in 30 instances and multiple in only 7. It was no surprise to learn that most of these were intimately exposed to open tuberculosis from earliest infancy. We discovered that known contact had existed before the third month of life in 18 patients and before the sixth month in 24. The age at first contact was beyond the sixth month or indefinite in the others. The contact was known to be very intimate, occurring daily during this period, in 24 of 37 for whom accurate data were available. Twenty-one of the contacts were known to have open

tuberculosis and 3 were said to have been arrested; we have not secured satisfactory information concerning the criteria by which the supposedly arrested status was established. Certainly, the development of a positive tuberculin test in an exposed infant is a far more delicate means of proving infectivity of a suspected or a supposedly arrested case than any other clinical or laboratory measures we can apply.

Our first knowledge of these appallingly long and intimate periods of exposure to open tuberculosis was secured at the time these patients were admitted for

TABLE 2
Tuberculosis in children
Features of terminal illness in 95 patients
Charity Hospital in New Orleans—ten years
A. Initial manifestations as they appeared chronologically

	FIRST	SECOND	THIRD	TOTAL
1. Fever.....	30	32	9	71
2. Cough.....	26	16	10	52
3. Intestinal.....	8	13	16	37
4. Meningeal.....	8	8	18	34
5. Weight loss.....	9	7	6	22
6. Glandular.....	3	2	1	6
7. Others.....	12	9	17	38

B. Duration of terminal illness

	FROM FIRST CONTACT	FROM FIRST SYMPTOM	BEFORE ADMISSION	IN HOSPITAL
Under 1 week.....	5	63	14	39
1-3 wks.....	2	17	38	40
1-3 mos.....	5	5	19	10
4-6 mos.....	13	8	11	2
7-12 mos.....	70	2	11	4
Over 1 yr.....			2	
Unknown.....	95	95	95	95
Total.....				

terminal hospitalization. In 20 of 37 patients, known duration of contact exceeded three months; in the others it lasted for a shorter or uncertain period. Other physicians or agencies may have made vigorous efforts to break such contacts, but from the meager data we have, this seems unlikely. Over two-thirds of these contacts were with one or both parents; the remainder were with grandparents or near relatives, and all but 2 were known to have occurred within the household. Whereas prolonged contact is not a necessary prerequisite for the development of fatal tuberculosis in infants and children, it certainly occurs in most instances and undoubtedly enhances the risk of such outcome.

Table 3 shows a consistently higher number of deaths in Negroes than in

whites. During the period of this study, 268 white children were admitted for clinical diagnosis of tuberculosis; 36 deaths among these represent a fatality rate of 13.4 per cent. In the same period 117 deaths occurred among 516 colored infants and children admitted for clinical diagnosis of tuberculosis, a fatality rate of 22.6 per cent. Explanations for these apparently disproportionate risks

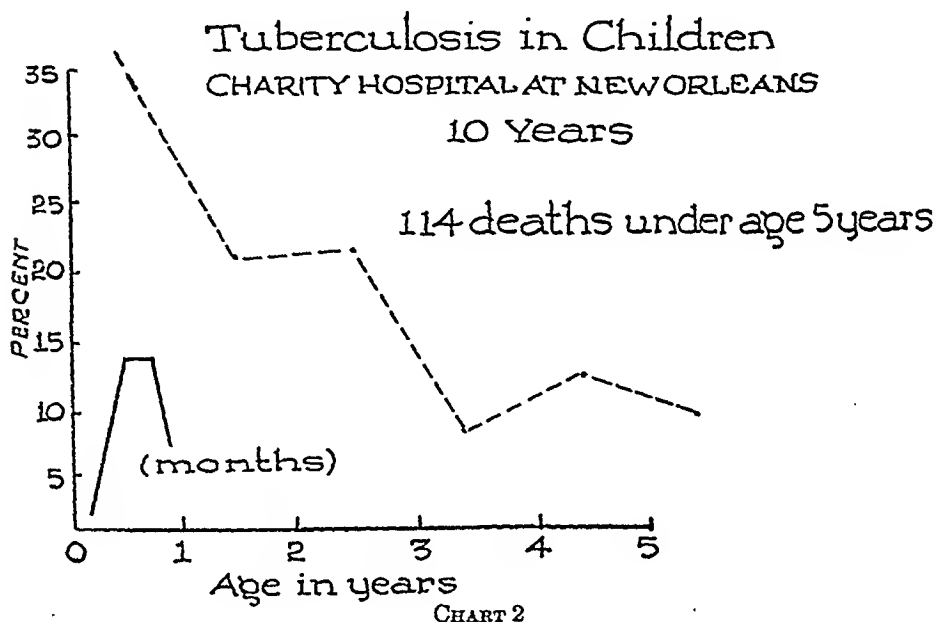


TABLE 3

Deaths from tuberculosis in white and colored children by age

AGE IN YEARS	WHITE	COLORED	TOTAL
Under 1	8	33	41
1	3	22	25
2	7	18	25
3	3	7	10
4	2	11	13
5-9	9	14	23
10-12	4	12	16
Total.....	36	117	153

for young Negro infants are not adequate at present. Thirty-three deaths in colored infants under one year represent 6.5 per cent of 516 admissions for tuberculosis in Negro children; in this same period only 8 white infants died, accounting for just 3 per cent of the total number of white patients. Sixty-eight per cent of all deaths in colored and 60 per cent of all deaths in white children occurred before the fourth year.

Recent experiences and observations, such as these, have further accentuated our anxiety over problems of prophylaxis, recognition and subsequent manage-

ment of *early* primary cases. Our studies indicate that routine premarital and prenatal tests for tuberculosis deserve at least equal weight with those for syphilis. Legislative action in the latter regard has effected a dramatic reduction in infantile forms of syphilis; perhaps a similar program would be equally effective in our attack on tuberculosis. The means are at hand, of proved merit and easily accomplished. Careful medical check-ups are a routine integral part of good obstetric practice; for reasons of maternal welfare these almost always include certain procedures for recognition of tuberculosis. In socio-economic circumstances favoring a high incidence of this disease, however, the advantages of such a program are frequently denied and, of course, it is in this unfortunate stratum that our most dismal experiences result.

Authoritative opinions regarding prognostic implications of early infection with tuberculosis are familiar to you all and only serve to intensify the concern I have previously expressed. The important reasons for such a dismal outlook are too well known to require repetition. There is no need at present for reopening the arguments regarding the relationship of allergy to immunity or entering into any controversy about implied protective virtues of a positive tuberculin test. I think we must all agree that, the earlier infection occurs, the more pessimistic and careful we must be in predicting its course. There is no place for complacency when one encounters a positively reacting infant or child.

The physician has at least six clear-cut responsibilities in this situation: he must classify or describe the lesion, judge activity, determine communicability, seek the source of infection, make recommendations for therapy based on specific objective data and, last, follow each patient carefully at frequent intervals at least until all evidences of activity have subsided or until resolution of the initial lesion is complete, as judged by discrete calcification. Certainly, the three-year period following the initial infection is most important. Careful classification or description is the best means for initiating his program; it is rank fallacy to believe that all asymptomatic tuberculin-positive children are necessarily in a benign category. Each patient must be studied carefully, and simple routine roentgenograms of the chest are not enough. Accepted, published nomenclature is familiar to most physicians; though weighted perhaps too heavily in favor of interpretation by roentgenographic means alone, it still has great merit.

Regardless of classification, activity must be measured by objective means we all use daily. Most of these, such as body temperature and weight, sedimentation rate of erythrocytes, total and differential leucocyte count and the ratio of monocytes to lymphocytes, can be influenced by a multitude of diseases other than tuberculosis. We often encounter clinical situations in which it is impossible to establish or differentiate causes for aberrations from normal values. When this occurs, the positively reacting child always deserves the benefit of doubt; evidences of activity should be ascribed to infection with tuberculosis until proved due to other cause.

When there are symptoms or evidences of activity attributable to tuberculosis of any form—primary or reinfection—an attempt should always be made to assess hazard to others. No exception is justified simply because we believe most cases classed as primary, meningeal or miliary are for practical purposes non-

communicable. Demonstration of acid-fast bacilli in sputum, gastric washings or feces constitutes a firm basis for instituting precautions well known to all medical workers.

We have repeatedly emphasized that as much, if not more, information can be gained by close questioning of patients or parents regarding probable contacts than by simply suggesting that conventional roentgenological studies be done. Following such perusal for the most likely contacts, routine tuberculin testing will favor more intelligent and economic use of roentgenological aids.

Limitations of the purely roentgenological method of case-finding are well known. Although roentgenograms play an all-important rôle in objectively discovering and delineating tuberculous lesions, they will never be accurate enough to supplant sound medical judgment. I raise this small voice not to decry the remarkable and praiseworthy strides that have been made toward increasing use of this instrument, but only to slow the tide of opinion implying that it may think, feel and hear as well as it sees!

Specific recommendations should follow logically when the case in question has been properly classified, activity and communicability assessed and contacts determined. It seems unnecessary to stress once again that doubtful features should be considered tuberculous until proved otherwise, that close supervision and frequent evaluation of activity are most important for three years following infection, and that specific means are at our disposal for preventing, avoiding or significantly attenuating each and all of the common hazards that arise during childhood. Most serious of these is reinfection or continuous contact, particularly during three years after the initial infection and during adolescence. Such factors as malnutrition, excessive fatigue, inhalation anesthetics and intercurrent diseases, particularly pneumonia, pertussis and measles, are equally well known.

The diligence of follow-up care must of course be individualized. Complete rest, modified or full activity should be justified by criteria of activity previously discussed. Discernible lesions should be reexamined at frequent intervals at least until resolution or discrete calcification has occurred. During this time all the talents of physician, nurse and social worker should be directed at correction of environmental causes, prevention of exogenous reinfection, maintenance of rest during any evidence of active infection, improvement of nutrition and physical condition and prevention or attenuation of dangerous intercurrent non-tuberculous infections.

Therapy for the primary infection is still nonspecific, employing well known concepts of protection from reinfection, rest as indicated by specific criteria, maintenance of the best possible nutritional status and education of patients and all members of their families in the nature of the disease and effective means for controlling its spread. Closer attention to time-proved measures can still further reduce the dangers of tuberculous infection in children until specific means for its eradication are available. It has been amply demonstrated that all our diligence and judgment directed at the control of primary tuberculosis are rewarded by a decreasing experience with some of the most desperate clinical problems in pediatrics.

R. V. PLATOU

SUMMARY

In an analysis of all deaths from tuberculosis at Charity Hospital of Louisiana at New Orleans during the last ten years, it was found that 9.8 per cent of the total deaths and 6 per cent of all deaths in children were attributable to this disease. Distribution of deaths by age and color, symptomatology, source of infection, features and duration of the terminal illness was tabulated. These studies accentuate our anxiety over problems of prophylaxis, recognition and management of *early* primary cases.

When a physician encounters an infant or child with a positive tuberculin test, he has six clear-cut responsibilities: he must classify or describe the lesion, judge activity, determine communicability, seek the source of infection, make recommendations for therapy based on specific objective data and, last, follow each patient carefully at frequent intervals at least until all evidences of activity have subsided or until resolution of the initial lesion is complete. Therapy for the primary infection is still nonspecific, employing well known concepts of protection from reinfection, rest as indicated by specific criteria, maintenance of good nutritional status and education of patients and all members of their families in the nature of the disease and effective means for controlling its spread.

SUMARIO

En un análisis de todas las muertes debidas a tuberculosis en el Charity Hospital de Louisiana de Nueva Orleans durante el último decenio, se observó que 9.8% de todas las muertes y 6% de todas las infantiles eran imputables a dicha dolencia. Tabuladas las muertes conforme a edad y color del enfermo, semiología, fuente de infección, características y duración de la enfermedad terminal, acentuáse la ansiedad infundida por los problemas de profilaxia, reconocimiento y atención de los casos primarios *tempranos*.

Cuando el médico encuentra a un lactante o niño con una reacción positiva a la tuberculina, tiene seis obligaciones bien definidas: debe clasificar y distribuir la lesión, justipreciar la actividad, determinar la transmisibilidad, buscar las fuentes de infección, formular recomendaciones terapéuticas basadas en datos específicos, y por fin, observar al enfermo cuidadosa y frecuentemente por lo menos hasta que hayan desaparecido todos los signos de actividad o hasta que se complete la resolución de la lesión inicial. La terapéutica de la infección primaria es todavía inespecífica, utilizándose los conocidos conceptos de protección contra la reinfección, el reposo según lo indican pautas específicas, el mantenimiento de un buen estado nutritivo y la instrucción de los enfermos y de todos los familiares en la naturaleza de la enfermedad y en los medios más efectivos para cohibir su propagación.

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PULMONARY FUNCTION FOLLOWING PNEUMOTHORAX^{1,2}

An Investigation of the Volume and Ventilation of the Lungs

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A relatively long time after the therapeutic value of pneumothorax treatment had gained general recognition, investigations were made of its physiological effect. In Germany these questions have been dealt with, among others, by Anthony and his coworkers, and in the United States especially by Cournand and Richards and coworkers. Very few investigations were made of pulmonary function after the conclusion of pneumothorax treatment. Cournand and Richards (1) carried out such investigations in 11 cases, which, on an average, showed a moderately reduced function. Potter (2) made a clinical study of the state after the conclusion of pneumothorax treatment and found fairly often X-ray changes in the form of thickened pleura, but more rarely functionally significant changes.

It is not unusual for a patient who has received pneumothorax treatment for pulmonary tuberculosis to be more troubled with dyspnea after the treatment than before. Especially is this the case if a pleurisy with effusion arose during the treatment and led to an obliterative pleuritis with retraction of the lung. If such changes are bilateral, the dyspneic state may be very troublesome and sometimes lead to complete invalidism. In connection with certain forms of pulmonary tuberculosis, dyspnea is common also without pleural complications, and in single cases it may often be difficult to determine the real cause of the dyspneic tendency.

Theoretically there are several alternatives that may give rise to the diminished respiratory reserve in such cases. The following causes are chiefly to be reckoned with:

- 1: Diminished available amount of parenchyma owing to the pathological process.
- 2: Development of emphysema of the so-called compensatory type owing to contraction of the pathological foci.
- 3: Changes involving reduced ventilatory efficiency of the uninvolved parenchyma (ventilatory insufficiency).

The first of these factors is generally reckoned with, but the second, compensatory emphysema, has come to occupy a very obscure place as a cause of respiratory insufficiency in pulmonary tuberculosis. When closer attention is paid to this factor, one finds that the majority of patients with chronic pulmonary tuberculosis are more or less affected by it, not infrequently with important consequences to their respiration. Finally, the changes leading to impaired ventilation are caused both by pleural retraction of the lung following pneumothorax treatment and by the tuberculous process in the lung.

In order to try to throw light on the quantitative importance of the functional

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impairment, often following in the wake of pneumothorax treatment, the following patients were studied:

- (a) 11 cases with completed pneumothorax treatment and with more or less prominent parenchymal and pleural changes, and
- (b) 25 patients with pleurisy with effusion who received pneumothorax treatment but who had no demonstrable parenchymal lesions, either before or after the treatment, and who, judging by the course of the disease, have complete pleural obliteration.

It should be possible in this way to get an idea of the impairment of function that may be caused solely by pneumothorax treatment when this has resulted in pleural obliteration and retraction, although the pleural changes in patients with pulmonary tuberculosis treated with pneumothorax are often considerably greater owing to the length of treatment, the nature of the effusion, etc. Pneumothorax treatment in cases of exudative pleuritis has, for some years, been tried in Sweden with the aim of attempting to reduce the large number of cases that later develop pulmonary tuberculosis. The results of this treatment, as compared with those of conservative treatment, are not yet clear.

METHOD

In order to study the functional reserve of the lungs, certain elementary physiological data were investigated; namely, the pulmonary volumina of the lung and the respiratory dead-space.

Other methods are available, but those employed here are sensitive tests that generally refer exclusively to the state of the lungs. They are, moreover, easily reproducible and are practically independent of the coöperation of the patient. Courmand and Richards (1, 3, 4) and Courmand and Berry (5) achieved good results with tests of the maximum breathing capacity, breathing reserve and their relation to each other. Although they do not fulfil the demands mentioned above, these tests are sufficiently encouraging to suggest further attempts along similar lines. Of the methods employed by these authors (6), the "pulmonary emptying rate," that is, the rapidity with which, during the inhalation of oxygen, the lungs eliminate nitrogen, is of particular interest as a criterion of the effectiveness of ventilation. It has important points of contact with the present writer's method for the estimation of the dead-space.

In the present investigation no working test has been employed, but it is doubtless along this line that tests of function will in future develop; study of the blood gases may be more informative than in the state of rest, when they may be normal, even in the presence of far advanced lesions.

As has been shown, among others, by Bohr (7), Lindhard (8), Christie (9), Hurtado and Boller (10), there is a definite relation between the various lung-volume components, which for normal individuals lies within rather narrow limits.³ Hurtado and his coworkers, during the 1930's, published a number of

³ The normal value, as found by the author (11) with the present method, for the share of the total volume (= lung volume on maximal inspiration) taken by the residual air (= lung volume on maximal expiration) was for men 22.7 per cent \pm 2.5 and for women 25.5

papers on pulmonary volumina and their variations under normal and pathological conditions; they studied ventilation in emphysema and pneumoconiosis (12, 13). They came to the conclusion that the relation between the residual and total capacity was a reliable indicator of respiratory efficiency. The higher this ratio was, the more marked was dyspnea. The present writer (11) was able to confirm this and also found that the same applies to the equilibrium capacity, and not only in emphysema but in all cases of impaired pulmonary function with tendency to dyspnea.

The author found that high ratios for (1) residual air over total volume and (2) equilibrium capacity over total volume are most frequently caused by inadequately ventilated portions of the lungs, in which, therefore, respiration is insufficient. This occurs in bronchiectasis, emphysema, in fibrotic or infiltrated parenchyma, in cavities, etc.

With the decrease of the lung volume during pneumothorax treatment, the normal relation between the subdivisions of the pulmonary volumina was retained, unless some large part of the lung was badly ventilated because of pleural adhesions or some other cause. It was, therefore, possible to establish a hypothesis implying that under various conditions the organism strives to retain the normal relations between the effective subdivisions of the lung. When functionally inferior air-spaces (cavities, infiltrated, indurated or emphysematous parts, etc.) are added to these effective volumina the result will be a raising of the relation between the parts in question and the whole. Such a rise is tantamount to impaired pulmonary function, and it is associated, as has been mentioned above, with a more or less pronounced tendency to dyspnea. Thus, if the absolute values of the pulmonary volumina indicate the quantitative measure of the lung volume investigated, the relative values give an indication of its ventilatory quality.

In so far as completed pneumothorax treatment entails any changes of the kind mentioned above (hypoventilation of certain parts through reduced mobility of the thorax and the diaphragm), it ought to be possible to demonstrate this by measuring pulmonary volumina. The absolute values, such as the vital and the total capacity, must also be of interest.

In addition, the respiratory dead-space has been determined according to the author's method (11) in order to ascertain the efficiency of ventilation under these conditions.⁴ The author has been able to show that an uneven ventilation, with the method used, has the same effect on the value for the dead-space as a real increase of the same.

per cent \pm 2.8, while the corresponding values of the equilibrium capacity (= lung volume following a normal expiration) taken by the tidal air were 48.4 per cent \pm 5.0 and 46.3 per cent \pm 6.0, respectively.

⁴ Eleven determinations of the dead-space carried out on 8 men yielded a mean value of 0.18 lt. (37° C., moist). The values varied between 0.13 and 0.26 lt. For women (5 determinations) a mean value of 0.11 lt., with a variation of the values between 0.09 and 0.14 lt., was obtained. The dead-space varied between 18 and 45 per cent of the tidal air, but was as a rule about 30 per cent. In cases with emphysema this figure generally exceeded 50 per cent; a value above this limit must be regarded as pathological.

The fasting patients were examined in a comfortable sitting position in the morning after a rest of about half an hour. After the vital capacity was determined, the equilibrium capacity was obtained in the following way: A mixture of hydrogen gas of known concentration and volume in a closed respiratory system with motor-driven circulation was allowed during ordinary, quiet breathing to distribute itself between the patient's lungs and the spirometer system. At intervals of exactly one minute, samples of the content of the spirometer were taken and analyzed for hydrogen. When a practically complete mixture of the gas was obtained and calculated volume of gas in the lungs was thus constant, the mean value of at least 3 samples was taken as the definitive measure of the volume of the lungs. For hydrogen-gas analysis the combustion method was used and a standard deviation for each determination of the lung volume of 89 ± 19 cc. was obtained. With the help of the values for the lung volume that were obtained every minute, it was possible to follow the course of the mixing of the intrapulmonary air with the gas of the spirometer system. As the other factors affecting this course were known, it was possible to calculate the dead-space that would give rise to such a course of mixing. The accuracy of this dead-space value varied, but in normal cases it was correct to within 0.01 to 0.02 lt. In cases with higher dead-space values, the limits of variation were greater.

For further details of the method the reader is referred to the original paper (11).

MATERIAL

The material examined comprises mainly patients from the medical tuberculosis department of St. Göran's Hospital.

Eleven of these patients had undergone pneumothorax treatment for pulmonary tuberculosis, 5 of these 11 having had pneumothorax on both sides. In several cases pleural effusion complicated the course of the treatment, and retraction of the lung often arose with—or even without—this cause. The nature of the parenchymal lesions varied, but the majority suffered considerable restriction of the functioning amount of parenchyma. Three patients had compensatory emphysema, confirmed in 2 cases on postmortem examination (cases 3 and 10). The cases are described in the case reports.

The other 25 patients had pleurisy with effusion without parenchymal changes; they had received so-called preventive pneumothorax treatment, usually for a period of one to two years, but in 9 of the cases the treatment was broken off earlier on account of obliterative pleuritis. In the majority of cases the treatment was carried out during the years 1942 to 1944. In 21 cases complete or almost complete collapse of the lung was obtained to start with, but 4 cases had, from the outset, such adhesions that the collapse was not so pronounced as retraction of the lung that resulted in these 25 cases was only moderate. The one seen in certain patients with pneumothorax treatment for pulmonary tuberculosis; it was generally restricted to obliteration of the costophrenic sulcus or a horizontal diaphragm with lateral fixation of the thoracic wall. More marked thickening of the pleura or greater retraction of the mediastinum to the treated side were seldom found. At the termination of treatment, the majority seems to have had complete obliteration of the pleural space.

RESULTS

A. *Pulmonary tuberculosis with completed pneumothorax treatment.* The cases investigated were purposely chosen to cover a wide variety of type and it will,

therefore, be necessary to describe them more in detail (table 1). Cases 1 and 4 had rather small lung lesions, and the pleural thickening was relatively slight, especially in case 1. In agreement with this, the absolute values of the pulmonary volumina were normal for the size of the body or only slightly diminished. One, therefore, expected a fairly normal function, and none of these patients suffered from dyspnea. In full agreement herewith, a normal value was found for the dead-space in case 4, where it was possible to determine it. In case 2, there was evident emphysema of compensatory type, which gave rise to the typical increase of the residual air, both as regards its absolute and relative values. The impaired function was clearly shown in the increased value of the dead-space. Dyspnea was a prominent symptom in this patient.

With the exception of cases 6 and 7, all the other cases showed a more or less pronounced tendency to dyspnea. To some extent this was probably due to far advanced parenchymal lesions but, especially in cases 9, 5 and 11, impaired ventilation (note the low vital capacity) was probably caused by bilateral pleural retraction, following pneumothorax. In case 9 there was an especially large dead-space indicative of emphysema.

Apart from the obviously pathological dead-space values in patients with emphysema (cases 2 and 9) the other cases showed no considerable deviation from the normal, though a certain rise of the absolute values may very well exist in the women. The relative dead-space value, which is normal, invites caution in interpretation.

As appears from table 1, the majority of the cases showed a definite decrease of the total lung volume and the vital capacity, as well as a very marked rise in the relative values of the residual air and equilibrium capacity. These rises indicate a markedly reduced function in accordance with the tendency to dyspnea. Although in certain cases it may be assumed that this impairment of function is largely due to the pleural changes, it is not possible to determine quantitatively the extent to which they have contributed to the impairment. A more detailed discussion of this point in connection with certain typical cases is given under the heading "Discussion."

B. Completed pneumothorax treatment in cases of pleurisy with effusion without parenchymal lesions: In order to decide whether the values of the pulmonary volumina are normal or not, a comparison is often made with calculated values. These values were calculated on the basis of the subject's body surface (which has been regarded as a function of height and weight (West (14)), his basal metabolic rate (Anthony (15)), or simply of his height or weight. The uncertainty of these calculations is considerable and a more reliable method is to compare the group presented here with a group of healthy persons. The latter procedure was applied in the present study. A group of healthy persons between the ages of 20 and 40, who had been previously examined (Birath (11)), were taken as the normal material.

The results of the investigations of the lung volume and its subdivisions in cases of pleurisy without parenchymal lesions are given in table 2.

The single cases in this group showed, on the whole, no considerable deviations from the normal which, on account of the relatively slight postpleuritic changes,

TABLE 1
Absolute and relative values of the pulmonary volumina and the dead-space value in 11 cases of pulmonary tuberculosis (5 males and 6 females) with completed pneumothorax treatment

CASE NUMBER	PULMONARY VOLUMINA						DEAD-SPACE VALUES		
	Absolute values in liters (37°C., moist)				Relative values in per cent of the total volume		Absolute values in liters (37°C., moist)		Relative value per cent of the tidal volume
	Equilibrium capacity	Residual air	Vital capacity	Total volume	Equilibrium capacity	Residual air	Dead-space	Tidal air	
Males									
1	3.76	1.74	5.36	7.10	53.0	24.5	0.47	0.84	56.0
2	3.04	2.18	2.64	4.82	63.1	45.2			
3	2.80	1.90	2.59	4.49	62.4	42.3			
4	2.33	1.07	3.58	4.65	50.1	23.0			
5	1.81	1.48	1.14	2.62	69.1	56.5	0.15	0.43	34.9
Females									
6	2.70	1.72	2.78	4.50	60.0	38.2			
7	2.59	1.70	2.86	4.56	56.8	37.3			
8	2.44	1.48	2.14	3.62	67.4	40.9	0.14	0.42	33.3
9	1.46	0.98	1.57	2.55	57.3	38.4	0.18	0.53	34.0
10	1.42	1.24	0.87	2.11	67.3	58.8	0.32	0.44	72.7
11	1.41	1.15	0.97	2.12	66.5	51.2	0.18	0.42	42.9

Case reports for table 1

Case 1: Terminated pneumothorax treatment for pleurisy with effusion on the right side with moderately advanced apical phthisis on the left. Obliteration of the right costophrenic sulcus. No dyspnea.

Case 2: Chronic contracting apical phthisis on the right side with a cavity the size of a walnut and scattered, fibrous foci. Considerable emphysema. Obliteration of the right costophrenic sulcus after pneumothorax treatment. Dyspnea ++.*

Case 3: Bilateral contracting apical phthisis with cavitation. Moderate emphysema (verified at autopsy). Considerable pleural thickening on the left and obliteration of the right costophrenic sulcus after bilateral pneumothorax treatment and effusion on the right. Dyspnea ++.*

Case 4: See figure 5.

Case 5: See figure 1.

Case 6: Chronic contracting apical phthisis with cavities. Obliteration of the right costophrenic sulcus and moderate pleural thickening after pneumothorax treatment with effusion. Dyspnea +.*

Case 7: Moderately advanced apical phthisis on the right side. Obliteration of the costophrenic sulcus after pneumothorax with effusion. Dyspnea +.*

* Dyspnea + = Moderate dyspnea on movement.
* Dyspnea ++ = Dyspnea even on slight exertion.

PULMONARY FUNCTION FOLLOWING PNEUMOTHORAX

TABLE 1—continued

Case 8: See figure 2.

Case 9: See figure 4.

Case 10. Far advanced, bilateral phthisis with cavities, localized mainly in the apices. Marked pleural thickening (exudate) over the left apex. Obliteration of the costophrenic sulci after bilateral pneumothorax treatment. Moderate emphysema (verified at autopsy). Dyspnea +++.*

Case 11: See figure 3.

* Dyspnea +++ = Dyspnea even at rest.

was not expected. In one single case (case 20), surprisingly high relative values were obtained (table 2). Experience has shown that such surprises are sometimes met with, especially in the case of uneasy and "nervous" female patients. These values are probably due to a heightened respiratory level and incomplete expiration caused by nervousness during the examination.

A group comparison with the normal material (tables 3 and 4) shows that the total capacity is diminished, both for the men (by about 23 per cent) and for women (by about 11 per cent). The same applies to the vital capacity (men, 27 per cent and women, 13 per cent). The equilibrium capacity, on the other hand, both for the women and the men, was not definitely changed. The residual air, again, was for the women about 22 per cent lower than the normal, but for the men it was not definitely diminished.

A statistical analysis was carried out separately for the men and women. The differences between the values for normal women and the postpleuritic group are shown in table 3. A statistically significant difference is found only in respect to the residual air, where the difference is equal to three times its standard error; but there was also a difference, which was probably of statistical significance in regard to the vital and the total capacity, where the difference exceeded two but not three times its standard error.

Since there were only 7 males, the classical method was not used for the statistical calculation, but instead, variance analysis (Snedecor's F-test). In this connection, it was proved that the probability (P) that a difference between the values was due to mere chance is, for the residual air, > 0.2 , indicating no significant difference; and for the equilibrium capacity, $0.05 < P < 0.2$, which is a statistically uncertain difference. For the vital and the total capacity the difference is statistically significant; in both cases $P < 0.001$ (table 4).

Concerning the relative values, the male cases showed an obvious increase in the ratio $\frac{\text{Residual capacity}}{\text{Total capacity}}$ and the female cases a slight tendency to increase, as compared with the normal values (tables 3 and 4). This tendency was confirmed by the more evidently increased values for the ratio $\frac{\text{Equilibrium capacity}}{\text{Total capacity}}$.

since an increase of one of these ratios was quite regularly followed by an increase of the other.

TABLE 2

Absolute and relative values of the pulmonary volumina and the dead-space value in 25 post-pleuritic cases (7 males and 18 females) with completed pneumothorax treatment

CASE NUMBER	PULMONARY VOLUMINA						DEAD-SPACE VALUES		
	Absolute values in liters (37°C., moist)				Relative values in per cent of the total volume		Absolute values in liters (37°C., moist)		Dead-space in percentage of tidal air
	Equi-librium capacity	Residual air	Vital capacity	Total volume	Equi-librium capacity	Residual air	Dead-space	Tidal air	
Males									
12	4.30	2.17	4.46	6.63	64.9	32.7			
13	3.14	1.34	4.54	5.88	53.4	22.8	0.24	0.59	40.7
14	2.85	1.64	3.39	5.03	56.7	32.6	0.27	0.63	42.9
15	2.68	1.14	4.09	5.23	51.2	21.8			
16	2.59	1.44	2.88	4.32	60.0	33.3	0.16	0.42	38.1
17	2.03	1.01	2.99	4.00	50.8	25.3	0.25	0.46	54.3
18	1.68	1.00	3.45	4.45	37.8	22.5			
Mean.....	2.75	1.39	3.69	5.08	51.7	27.3			
Females									
19	2.98	1.48	4.03	5.51	54.1	26.9	0.18	0.44	40.9
20	2.86	2.33	1.69	4.02	71.1	58.0	0.17	0.41	41.5
21	2.78	1.38	3.50	4.88	57.0	28.3	0.13	0.51	25.5
22	2.73	1.30	3.07	4.37	62.5	29.7	0.31	0.67	46.3
23	2.73	1.47	3.82	5.29	51.6	27.8	0.10	0.44	22.7
24	2.57	1.14	3.77	4.91	52.3	23.2			
25	2.47	1.47	3.45	4.92	50.2	29.9	0.32	0.59	54.0
26	2.32	1.23	3.22	4.45	52.1	27.6	0.34	0.66	52.0
27	2.26	0.73	3.11	3.84	58.9	19.0			
28	2.24	1.04	3.30	4.34	51.6	24.0	0.22	0.53	41.5
29	2.13	1.01	3.40	4.41	48.3	22.9			
30	2.13	1.13	3.50	4.63	46.0	24.4	0.14	0.29	48.3
31	1.95	0.72	3.11	3.83	50.9	18.8			
32	1.91	1.13	2.95	4.08	46.8	27.7			
33	1.63	1.03	2.55	3.58	45.5	28.8			
34	1.51	0.62	3.22	3.84	39.3	16.1			
35	1.36	0.77	1.80	2.57	52.9	30.0			
36	1.26	0.90	2.22	3.12	40.3	28.8			
Mean.....	2.21	1.16	3.10	4.26	53.5	27.3			
Standard error of the mean.	±0.12	±0.09	±0.15	±0.17	±3.2	±2.0			

The difference between normal men and the cases under investigation in regard to the ratio $\frac{\text{Residual air}}{\text{Total capacity}}$ is most likely statistically significant, because covari-

ance analysis shows that: $0.001 < P < 0.01$. As regards the women, however, it was not possible to establish a statistically significant difference ($P > 0.2$). Between the women under investigation and normal women a statistically most likely significant difference exists for the ratio $\frac{\text{Equilibrium capacity}}{\text{Total capacity}}$, since: $0.001 < P < 0.01$. For men this difference was only probably significant, since: $0.01 < P < 0.05$. (See chart 1.)

TABLE 3

Differences between mean values of the pulmonary volumina in 19 normal and 18 postpleuritic patients (females)

CASES (FEMALES)	ABSOLUTE VALUES IN LITERS (37° C., MOIST)				RELATIVE VALUES IN PER CENT OF THE TOTAL VOLUME	
	Equilibrium capacity	Residual air	Vital capacity	Total volume	Equilibrium capacity	Residual air
Normal (19)....	2.22 ±0.11	1.49 ±0.06	3.57 ±0.10	4.79 ±0.15	46.3 ±1.4	25.5 ±0.7
Postpleuritic (18).....	2.21 ±0.12	1.16 ±0.09	3.10 ±0.15	4.26 ±0.17	53.5 ±3.2	27.3 ±2.0
Difference and ± standard error of the difference...	0.01 ±0.16	0.33 ±0.11	0.47 ±0.18	0.53 ±0.23	-7.2 ±3.49	-1.8 ±2.12

TABLE 4

Differences between mean values of the pulmonary volumina in 16 normal and 7 postpleuritic patients (males)

CASES (MALES)	ABSOLUTE VALUES IN LITERS (37° C., MOIST)				RELATIVE VALUES IN PER CENT OF THE TOTAL VOLUME	
	Equilibrium capacity	Residual air	Vital capacity	Total volume	Equilibrium capacity	Residual air
Normal (16)....	3.18 ±0.11	1.49 ±0.06	5.08 ±0.12	6.57 ±0.15	48.4 ±1.2	22.7 ±0.6
Postpleuritic (7).....	2.75	1.39	3.69	5.08	51.7	27.3
Difference....	0.43	0.10	1.39	1.49	-3.3	-4.6

The results were also grouped according to the character of the roentgenologically demonstrable pleuritic changes. The first group comprised those cases which, following pneumothorax treatment, showed only slight residual pleurisy, such as obliteration of the costophrenic sulcus, possibly in combination with somewhat thickened pleura and, in some cases, minor apical pleural thickening (14 cases). In the second group were those cases in which, due to adhesions to the thoracic wall, the diaphragm had assumed a practically horizontal position (4 cases). The third group comprised the 7 cases with the greatest changes, but even these showed only moderate pleural retractions.

A comparison between the first and the third group showed that a reduction

of all capacities had taken place in the third group, while the relative lung-volume values did not show any differences between the groups.

EQUILIBRIUM CAPACITY LITERS

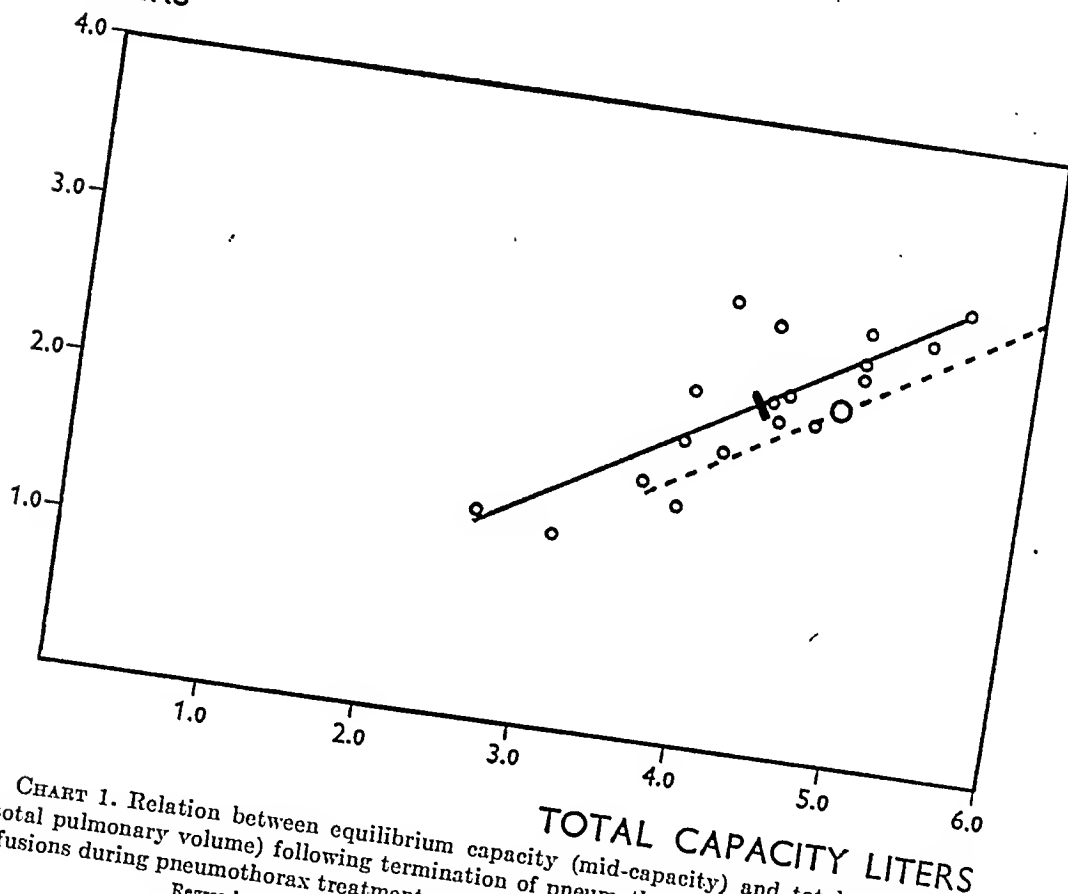


CHART 1. Relation between equilibrium capacity (mid-capacity) and total capacity (total pulmonary volume) following termination of pneumothorax in 18 women who had effusions during pneumothorax treatment.

Regression line and mean value	Regression equation	Regression coefficient	Correlation coefficient
Normal females (not plotted) ... ---○---	$Y = 0.60 X - 0.65$	0.60 ± 0.12	0.78 ± 0.09
Females who had pleural effusions (0)..... —+—	$Y = 0.59 X - 0.29$	0.59 ± 0.10	0.83 ± 0.07

It was found, by variance analysis, that the total capacity, as well as the vital and equilibrium capacities, showed a probably significant difference ($0.01 < P < 0.05$), while for the residual capacity the difference was only possibly significant ($0.05 < P < 0.2$).

In other respects, the material proved to be too small to permit an investigation of the effect produced by the length of the period of treatment, which may,

of course, be thought to entail variations in function after conclusion of treatment. The same applies to the significance of symptoms (pain, fever, etc.) occurring a considerable time before thoracocentesis and the induction of pneumothorax, the occurrence of larger amounts of fibrin in connection with the initial thoracoscopy, the degree of the initial collapse, due to adhesions, etc.

If we now turn to the values of the respiratory dead-space, we find that these generally showed somewhat higher values than can be considered completely normal, indicating an impaired ventilatory economy. The values are too few in number to permit a statistical analysis with men and women separately or in any subgroups, but the general tendency to an increase of both the absolute and the relative values (in relation to the tidal volume) seems nevertheless clear. (Compare with the normal values mentioned above.)

DISCUSSION

What, then, is the importance of these results of studies on patients who were treated with pneumothorax for pleurisy with effusion? The cause of the diminished vital and total capacity is clear. It is perfectly natural that the adhesions between the pleural surfaces which usually follow this treatment should cause a reduction of these two capacities, which require full freedom of movement for the lung if they are to attain their maxima. At the same time, it may be observed that, in spite of relatively slight roentgenological pleural changes and with usually inconspicuous retraction, the lung capacities investigated were evidently affected, probably chiefly due to the impaired motion of the diaphragm, but also on account of some reduction of thoracic mobility caused by adhesions between the pleural surfaces.

It is of great interest that equilibrium and residual capacities increased in their relation to the total capacity, and that their absolute values changed less. The hypothesis already mentioned seems to supply a satisfactory explanation for the increase in the relative values. It also facilitates the understanding of the cases investigated.

One must assume that in cases with pleural symphysis and especially with diaphragmatic adhesions to the thoracic wall relatively large parts of the lungs are not as effectively ventilated as the rest of the lung. These parts or "pockets" of the lung are functionally inferior on account of hypoventilation. Conditions exist for a similar increase of the relation of the equilibrium capacity and residual air and the total capacity, as that which has been shown to develop with intrapulmonary changes. As this investigation has shown, such a change in the values under discussion actually does arise and this provides valuable support for the correctness of the hypothesis.

The cause of the rise in the dead-space value that has been demonstrated must be the same as that of the increased relative lung-volume values; namely, the reduced ventilation in certain parts of the lung. For it was proved empirically (for example in bronchostenosis) that a delaying of the gas mixing in the lung by uneven ventilation has the same effect on the dead-space value as an enlarged dead-space. This was proved also theoretically by the author (11).

Otherwise, this absolute and relative increase of the dead-space value occurs most commonly in cases with real enlargement of the respiratory dead-space in emphysema. There is, in general, no direct reason for suspecting emphysema in the cases of pleurisy investigated here; but one of the highest values (in case 25) can, nevertheless, be explained in this way, since between the ages of 8 and 20 the patient had suffered from typical bronchial asthma. In the other cases with particularly high values (cases 22 and 26) this cause is absent, but in the first of these there is according to the roentgenogram, probably following strumectomy in 1938, a tracheal stenosis that has given rise to a distention of the lung and, in this way, to the increased dead-space value.

In cases in which pleural symphysis has arisen following pneumothorax treatment, this must have its share in the impairment of function that appears with a heightening of the relative lung-volume values also when infiltrative or durative intrapulmonary processes act in the same direction. The methods employed do not, however, permit distinguishing between the effects of the two factors. In the single case it may be very difficult, without the support of roentgenograms and other clinical facts, to decide whether the essential cause of the impairment of function is, emphysema, intrapulmonary fibrosis or hy-poventilation of a relatively normal parenchyma, caused by reduced mobility of thorax and diaphragm.

To some extent radiography affords a certain guidance in this connection. In cases without parenchymal changes, the roentgenologically visible pleural changes are rather slight; in agreement with this, only minor changes in the relative lung-volume values have occurred. It is different in cases with parenchymal lesions. As is evident from the case reports, the majority of cases had considerable or severe dyspnea and, in agreement herewith, marked increases are found in the values of the relative lung volumina. As example, see case 5 in table 1. The X-ray picture (figure 1) shows unexpandable lungs with bilateral adhesions between the diaphragm and the thoracic wall, and encapsulated effusions. In the parenchyma of the upper lobes contracting lesions are present, but the lower lobes appear relatively normal. It is, therefore, probable that the

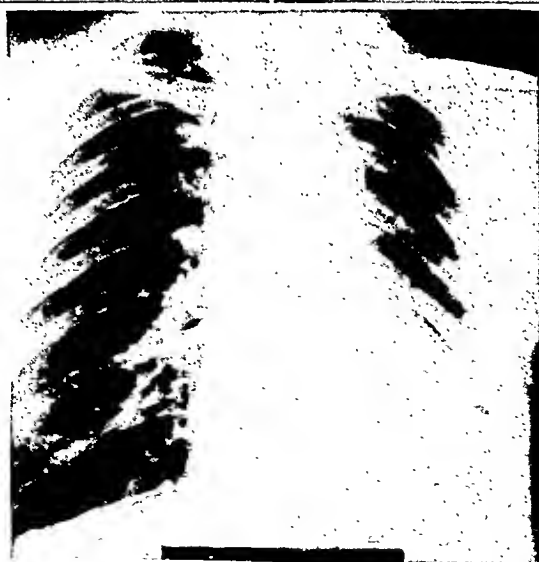
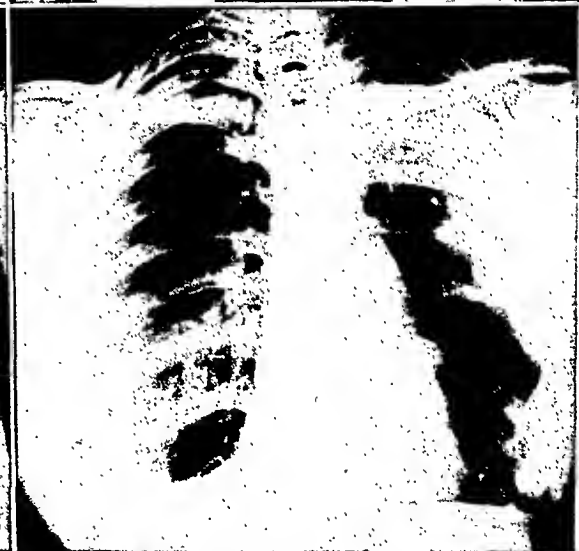
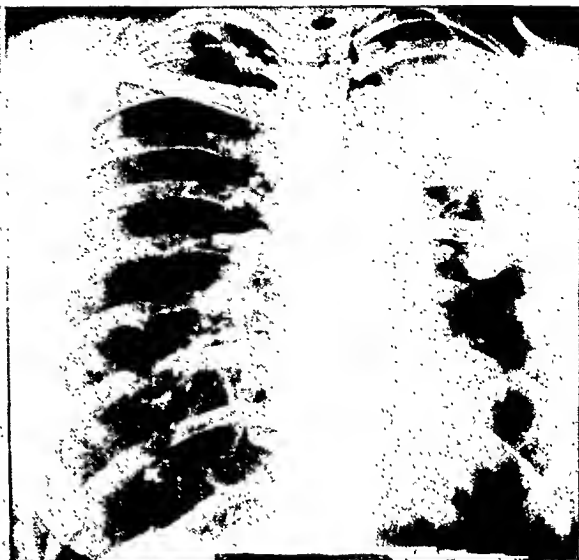
Fig. 1. (Case 5.) (Upper left.) Marked ventilatory insufficiency, pleurally conditioned. Chronic phthisis on the right side with cavitation, 2 to 3 cm. in diameter. Apical fibrous phthisis on the left side. Considerable pleural effusions in layers, 4 to 5 cm. in width on both sides (unexpandable lungs) after pneumothorax with effusions during reexpansion. Dyspnea ++.

Fig. 2. (Case 8.) (Upper right.) Contraction of the right upper lobe owing to broncho-stenosis and distention of the middle and lower lobes. Thickening of the pleura and retraction of the left lung after pneumothorax with effusion during reexpansion. Dyspnea ++.

Fig. 3. (Case 11.) (Centre left.) Ventilatory insufficiency of pleural origin. Contracting phthisis in the right apex with small cavities. Obliteration of the costophrenic sulci with elevation of the diaphragm laterally on both sides after bilateral pneumothorax with effusion on the left side. Dyspnea +++.

Fig. 4. (Case 9.) (Centre right.) Compensatory emphysema and marked ventilatory insufficiency after bilateral pneumothorax and oleothorax treatment, causing retraction of the lungs and reduced mobility of the diaphragm. Dyspnea ++.

Fig. 5. (Case 4.) (Lower.) Basal retraction of the left lung after pneumothorax treatment. Only slight functional impairment. No dyspnea.



ventilatory insufficiency is largely caused by the pleural changes. Both the low total capacity and the increased relative lung-volume values would indicate this.

In another case (no. 8, table 1), dyspnea also arose, for which the roentgenogram afforded a fairly adequate explanation. It (figure 2) showed a considerable retraction of the left lung as a sequela to earlier pneumothorax treatment. In addition, probably due to bronchostenosis, the right upper lobe is maximally contracted and, in the main, only the right lower and middle lobes appear to have parenchyma capable of functioning. It, therefore, seems understandable that both a considerable decrease of the total capacity and an increase of the relative values have developed. Probably on account of a distention of the functioning parenchyma and hypoventilation of other parts, the dead-space value is somewhat larger than usual in women. The relative value, however, is fairly normal.

In case 11 (table 1) with a very small total capacity and with very high relative lung-volume values, parts of both lungs are shrunken and the diaphragms are elevated and adherent to the lateral chest wall, as a residue following earlier bilateral pneumothorax treatment. The extensibility of the lung is evidently much reduced, perhaps, above all, on account of adhesions between the diaphragm and the thoracic wall (figure 3). At the time of examination, the intrapulmonary changes seemed to be of only moderate functional importance; the patient's pronounced tendency to dyspnea was probably largely caused by pleural adhesions which mainly account for her ventilatory insufficiency. The patient died after an acute exacerbation, and the postmortem examination seemed to confirm this assumption. The moderate increase of the dead-space value was apparently due to the same cause.

In other cases presented in table 1 the roentgenogram affords less guidance for estimating function. Case 9 was referred to me for examination because of dyspnea and a roentgenogram (figure 4) which was not considered to explain her dyspnea. Earlier she had had pneumothorax on both sides, which was followed by oleothorax. Later on the oil had been largely aspirated or absorbed. Spirometric examinations showed that the total capacity was low and that the relative values were much increased, indicating impaired function of the lung volume measured. The dead-space value was also abnormal, especially the considerable increase of the dead-space in percentage of the tidal volume, which was 72.7. A markedly impaired pulmonary function, with the expectation of dyspnea, was thus demonstrated, in a certain contrast to the roentgenogram. On the basis of the examination, the patient received the invalid's pension for which she was applying. The cause of her impaired function was probably in part reduced ventilation of the still functioning parenchyma, in part so-called compensatory emphysema in the same lung due to marked contraction of the previously involved parts. The oxygen saturation of the arterial blood, at rest, was maintained at 92.7 per cent.

At times, the roentgenogram may show changes indicative of more seriously impaired function than that actually existing. Case 4 (figure 5) showed retrac-

tion of the left base which led to the assumption of a considerable hypoventilation. Some reduction of the total capacity was observed as a sign of this retraction, but the relative values were fairly normal and did not indicate the existence of any important hypoventilated portions of the lung. For one reason or another, the retraction which roentgenologically appears to be of considerable degree, is functionally of lesser importance. The patient was not troubled with dyspnea.

Dyspnea in patients without parenchymal lesions was slight, at times very slight, in agreement with the relatively mild pleural changes as seen on the X-ray films; only slight disturbances of pulmonary function were demonstrated in these patients. In one case (no. 35) there was a higher degree of retraction, and in this patient, dyspnea was more pronounced. In none of these cases, however, did dyspnea interfere with their capacity for work.

PRACTICAL CONSIDERATIONS

Since this investigation has shown that evident impairment of pulmonary function occurs even with relatively slight retractions, and since the retractions which occasionally appear after pneumothorax treatment of pulmonary tuberculosis interfere to a high degree with respiratory function, the question arises whether marked retractions can be avoided.

In many cases, an effusion during pneumothorax treatment may give rise to the changes under discussion. In at least some of these cases, the more extreme degrees of retraction may probably be avoided if, in the presence of a prolonged effusion, pneumothorax treatment is terminated in time. Since obliterative pleuritis often develops in these cases, which will gradually render further treatment impossible, and since the risk of empyema is relatively great in precisely these cases, the decision to replace pneumothorax treatment with some other form of collapse therapy should be facilitated. There is also reason to believe that, with extended indications for primary apical thoracoplasty, a number of troublesome complications of pneumothorax treatment may be avoided. This change in the indications for treatment should be to the advantage of pulmonary function, although at first glance the contrary might appear to be the case. Apical thoracoplasty causes a relatively slight reduction of function. Cournand and Richards (1) state the advantage from the standpoint of physical capacity of substituting a good thoracoplasty for a poor pneumothorax. In favorable cases, the greater part of the parenchyma of the inferior lobe can be spared, and if there is, above all, good diaphragmatic mobility, the operated side can manage a large part of the respiratory gas exchange. There would not appear to be much prospect of succeeding, with so-called rational treatment of exudates and continued pneumothorax, in escaping the threatening reduction of function.

A further group of cases in which there is the threat of impairment of function comprises those in which lung retraction appears without effusion. In connection with pneumothorax refills, one then finds initial pressures which more and more tend in the negative direction, and the interval between the refills may be made longer and longer without the lung being expanded. Several of the above-

described cases have been of this type. Also in such cases, therefore, other collapse therapy should eventually be considered in good time.

SUMMARY

Twenty-five patients with pleurisy with effusion without parenchymal lesions, and in whom so-called preventive pneumothorax treatment had been terminated, were examined by the author's method for the estimation of the total lung volume and its subdivisions and of the respiratory dead-space. The following results were obtained:

1. Total and vital capacities were diminished.
2. Equilibrium and residual capacities were not generally diminished to the same degree, and their share in the total capacity was thus increased.
3. While the diminished total and vital capacities were due to the impairment of the thoracic and diaphragmatic mobility through pleural adhesions, the cause of the increased relative lung-volume values was a hypoventilation of certain parts of the lung, provoked by the same cause.
4. In 11 cases of terminated pneumothorax treatment chosen to throw light on the subject, and with more or less extensive parenchymal lesions, the following was found:
 1. The lung function, in several cases, was seriously impaired, manifesting itself in low total and vital capacities, considerable increase of the relative lung-volume values and in certain cases increased values for the respiratory dead-space.
 2. The cause of this was, in some cases, in part parenchymal contraction with so-called compensatory emphysema and reduction of the parenchyma, but in the majority of cases the cause was pleural changes following pneumothorax treatment (ventilatory insufficiency).
 3. In view of the very serious impairment of function that may result when a lung retraction complicates pneumothorax treatment, it is suggested that in certain cases this treatment should be abandoned and replaced with other collapse measures.

SUMARIO

- A 25 enfermos que padecían de pleuresía con derrame sin lesiones parenquimáticas y en los que había terminado el llamado neumotórax terapéutico preventivo, se les examinó con la técnica del autor para calcular el volumen pulmonar total y sus divisiones y el espacio respiratorio obliterado.
1. Hubo disminución de la capacidad total y la vital.
 2. En general no disminuyeron en grado igual la capacidad equilibradora y la residual, de manera que aumentó la participación de las mismas en la capacidad total.
 3. Aunque la disminución de la capacidad total y vital se debió a haber atenuado la movilidad torácica y diafragmática las adherencias pleurales, la causa del relativo aumento de los valores del volumen pulmonar fué una hypoventilación de ciertas partes del pulmón provocada por la misma causa.

En 11 casos de neumotórax terapéutico terminado que se escogieron para lanzar luz sobre el asunto y con lesiones parenquimáticas más o menos extensas observóse lo siguiente:

4. La función pulmonar en varios casos se afectó gravemente, traduciéndose esto por capacidades total y vital bajas y considerable aumento de los valores relativos del volumen pulmonar y en ciertos casos por aumento en la proporción del espacio respiratorio obliterado.
5. La causa de esto fué en algunos casos en parte la contracción parenquimática con el llamado enfisema compensador y reducción del parénquima, pero en la mayoría consistió en alteraciones pleurales consecutivas al neumotórax terapéutico (insuficiente ventilación).
6. En vista de la gravísima insuficiencia funcional que puede sobrevenir cuando una retracción pulmonar complica el neumotórax terapéutico, en ciertos casos convendría abandonar este tratamiento suplantándolo con otros métodos de colapso.

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STUDIES IN CHEMOTHERAPY OF TUBERCULOSIS^{1,2}

VIII. The Comparative Action of Four Sulfones in Experimental Tuberculosis in Guinea Pigs and the Combined Action of Streptomycin with One of the Sulfones

M. I. SMITH, Wm. T. McCLOSKEY AND E. L. JACKSON

It was shown previously (4) that streptomycin and sodium *p,p'*-diaminodiphenylsulfone-*N,N'*-didextrosulfonate (promin) mutually potentiated each other when applied together in the treatment of guinea pigs infected with tuberculosis. It seemed probable that the synergism would hold for other sulfones as well and consequently work has been in progress in an attempt to find a sulfone less toxic and if possible more effective than promin.

The present paper is a report of such a study with three sulfones which have become available to us in sufficient quantity. These were studied for chemotherapeutic efficacy in comparison with promin. At the same time the combined effect of streptomycin with one of the sulfones was also studied. The supply of streptomycin was limited and it was not possible to study the effect of this drug alone under the same experimental conditions.

The compounds we were able to study in the present investigation were:

- I. Sodium salt of 4-amino-4'-galacturonylaminodiphenylsulfone (galacturonide), prepared in the laboratories of Endo Products Co. and supplied by Dr. Samuel M. Gordon.
- II. 4-Amino-4'-ureidodiphenylsulfone (carbamyl), synthesized in the laboratories of Schering Corporation and supplied by Dr. Erwin Schwenk.
- III. 4-Amino-4'-*n*-propylaminodiphenylsulfone (*n*-propyl), synthesized in this laboratory by the reaction of *n*-propyl bromide with 4,4'-diaminodiphenylsulfone, the details of the procedure having been supplied by Dr. L. A. Sweet, Parke, Davis and Co.
- IV. Sodium *p,p'*-diaminodiphenylsulfone-*N,N'*-didextrosulfonate (promin), supplied by Parke, Davis and Co. The streptomycin used in this study was generously supplied by Charles Pfizer and Co. and Eli Lilly and Co.

EXPERIMENTS

A series of 120 guinea pigs, weighing about 300 to 350 grams, were inoculated intraperitoneally with 0.5 mg. of a homogeneous suspension of human tubercle bacilli H37Rv³ per cc. of sterile saline, and were divided into six equal groups of 20 as follows:

Group A: Treated with streptomycin, 10,000 units per kg. intramuscularly twice daily, 9 a.m. and 4 p.m., plus 0.15 to 0.3 g. per kg. of the galacturonide given orally once a day.

¹ From the Division of Physiology, National Institute of Health, Bethesda, Maryland.

² Other papers in this series are enumerated under References (1, 2, 3, 4, 5, 6, 7).

³ The culture was furnished by Mr. Wm. Steenken, Jr., Committee on Chemotherapy of Tuberculosis, National Tuberculosis Association; Dr. Leroy U. Gardner, Trudeau Sanatorium, Chairman.

Group B: Treated with 0.15 to 0.3 g. per kg. of the galacturonide, as above, but without streptomycin.

Group C: Treated with 0.3 to 0.5 g. per kg. promin, given orally once a day. This group served as a reference standard for comparison of the efficacy of the other sulfones.

Group D: Received 0.5 g. per kg. of the carbamyl derivative orally once a day.

Group E: Received 0.5 g. per kg. of the n-propyl derivative orally once a day.

Group F: Untreated controls.

The treatment, begun the day after infection, was carried out regularly five days a week, with a double dose on the fifth day, for a period of nine weeks. Daily dosage in the first three groups was planned to be 0.3 g. per kg. for groups A and B and 0.5 g. per kg. for group C, which are equivalent when computed on the basis of diaminodiphenylsulfone content. However, it was necessary to reduce them to 0.15 and 0.3 g. per kg., respectively, for a few days at intervals on account of drug toxicity as evidenced by excessive loss of body weight. Dosage in groups D and E was uniformly maintained at 0.5 g. per kg. There was no evidence of toxicity from these latter compounds at any time.

All treatment was discontinued sixty-three days after infection. At ninety days after infection all the survivors were tuberculin tested, using 0.01 mg. PPD in 0.1 cc. salt solution intracutaneously. The reactions were recorded twenty-four and forty-eight hours after injection. At 98 to 103 days after infection all the survivors were killed with chloroform, autopsied, and the extent of tuberculous involvement noted and rated on the basis of 0 to 4 in the organs and tissues of predilection as previously described (2), with a possible maximum of 20. In cases of doubtful lesions smears were made of the suspected materials and stained with Ziehl-Neelsen stain for microscopic examination and when feasible suspensions of the material in sterile saline were inoculated into the right groin of each of 2 guinea pigs for tuberculin testing and postmortem examination after an incubation period of six weeks.

RESULTS

The virulence of the strain and magnitude of dosage used were such as to produce in the controls extensive generalized tuberculosis of the viscera (with ascites and pleural and pericardial effusions in many cases), within thirty to forty days, and death of 95 per cent of the animals within seventy-five days of the infection. The average tuberculosis index for this group was 16.3, with a range of 9 to 20, out of a possible maximum of 20.

Ninety-five per cent of the animals of group A, treated with streptomycin and the galacturonide, were in excellent condition and gaining weight at the time the experiment was terminated, about 100 days after infection, and after a period of nearly forty days without treatment. One of the animals in this group died within twenty-four hours following the intracutaneous injection of PPD; this should be regarded as a tuberculin allergy death, since this animal had been in good condition, and since many in this group (95 per cent) gave positive tuberculin reactions. Postmortem examination of the animals in this group revealed no gross evidence of tuberculosis, or doubtful and negligible

TABLE 1
Effect of treatment with streptomycin and galacturonide in guinea pigs infected with 0.5 mg. H37Rv intraperitoneally
 Treatment continued sixty-three days. Killed 100 days after infection

NUM- BER	WEIGHT, GRAMS		PPD	ORGANS INVOLVED	TUBER- CULOSIS INDEX	SMEARS	SUBINOCULATION TESTS	
	Initial	Final					Tissue suspension	Result
1	390	604	2+	Small omental lymph node and few doubtful pin-point lesions in liver and lung	±	Negative		
2	382	672	+	None	0			
3	396	628	2+	None	0			
4	382	644	+	None	0			
5	340	616	2+	Small omental lymph node	±	Negative	Spleen	Positive
6	394	764	+	None	0		Spleen and lymph node	Positive
7	402	800	2+	None	0			
8	308	696	+	None	0		Spleen	Positive
9	252	580	2+	Doubtful spleen (1.6 g.)	0		Spleen and lung	Positive
10	318	420	3+	Minimal lesions in omentum, liver, lung, and peritoneum	±	Negative	Spleen and lung	Positive
11	334	500	Died	Minimal lesions in omentum, liver and lung	2		Spleen	Positive
12	310	520	+	Few military tubercles in lungs	3			
13	376	704	2+	None	1			
14	354	612	+	Small (5 mm.) consolidated area in upper right lobe	0			
15	382	680	±	Small omental lymph node	±	Negative	Spleen and lung	Positive
16	332	632	+	Doubtful few military lesions in liver and lung	±	Negative		
17	326	618	+	Minimal lesions in omentum, spleen and liver	1		Spleen and lung	Positive
18	328	628	+	None	2		Spleen	Positive
19	354	684	+	None	0			
20	336	624	+	Small necrotic omental lymph node	0		Spleen	Positive
					±	Negative	Spleen and lung	Negative

lesions in 75 per cent,⁴ and only minimal lesions in the remainder. However, subinoculation of spleen or other tissue suspensions into the inguinal region of

⁴ Animals with a tuberculosis index rating of 0 or ±.

normal guinea pigs resulted in positive PPD reactions and glandular involvement at the site of inoculation in all but one of the animals tested. A detailed summary of the findings in this group is given in table 1.

Table 2 and figure 1 show the results in summary form of the entire experiment. It will be seen that, at the dosage levels used, all the sulfones retarded the disease process to about the same degree as promin. The mortality rate was distinctly

TABLE 2

January 3, inoculated 0.5 mg. H57Rv intraperitoneally. Treatment begun January 4 and continued till March 8, sixty-three days. Tuberculin tested (.01 mg. PPD intracutaneously) April 3, twenty-six days after discontinuing treatment. Experiment terminated April 12 to 16, 98 to 103 days after infection




GROUP AND DRUG	A STREPTOMYCIN + GALACTU- RONIDE	B GALACTU- RONIDE	C PROMIN	D CARBAMYL	E N-PROPYL	F CONTROLS
Dosage in units or grams per kg. per day.....	2 × 10,000 +0.15-0.3	0.15-0.3	0.3-0.5	0.5	0.5	0
Mortality per cent at 63 days, end of treatment period.....	0	35	15	40	15	80
Mortality per cent at termina- tion of experiment, 98-103 days	5	70	40	50	40	95
Number reacting to PPD in re- lation to survivors 90 days after infection.....	18/19	6/8	13/13	9/10	12/14	1/1
Number losing weight in rela- tion to survivors at termina- tion of experiment.....	0/19	1/6	3/12	5/10	4/12	1/1
Tuberculosis Index						
Range.....	0-3	0-13	0-18	3-11	0-15	9-20
Mean.....	0.6	5.9	6.2	6.2	5.8	16.3
Spleen weight, grams						
Range.....	0.8-2.1	0.6-11.3	0.7-13.9	1.3-5.9	1.0-8.8	0.9-9.2
Mean.....	1.3	2.9	3.2	2.4	2.4	5.5
Average weight gain in grams...	281	41	148	161	172	17
Per cent with doubtful or no lesions.....	75	5	15	0	10	0
Chemotherapeutic effectiveness (ratio of extent of tuberculous involvement in controls and treated groups).....	100/3.7 27.0	100/36.2 2.7	100/38.0 2.6	100/38.0 2.6	100/35.6 2.8	




higher in the galacturonide group than in the promin or the other sulfone groups, and this may be due in part to the higher toxicity and, possibly the greater cumulative action of this compound. It is significant that the animals in group A, receiving the same amount of this drug in addition to streptomycin, were not affected in the same manner.

The chemotherapeutic effectiveness of the several compounds studied, expressed as the ratio of extent of tuberculous involvement in the controls and treated groups ranged from 2.6 to 2.8 for the four sulfones and 27.0 for the group

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treated with streptomycin and the galacturonide. Since there was no group in this series receiving streptomycin alone it is not possible to appraise accurately

A. STREPTOMYCIN + NH₂  SO₂  NH-C(=O)--O-

B. NH₂  SO₂  NH-C(=O)--O-

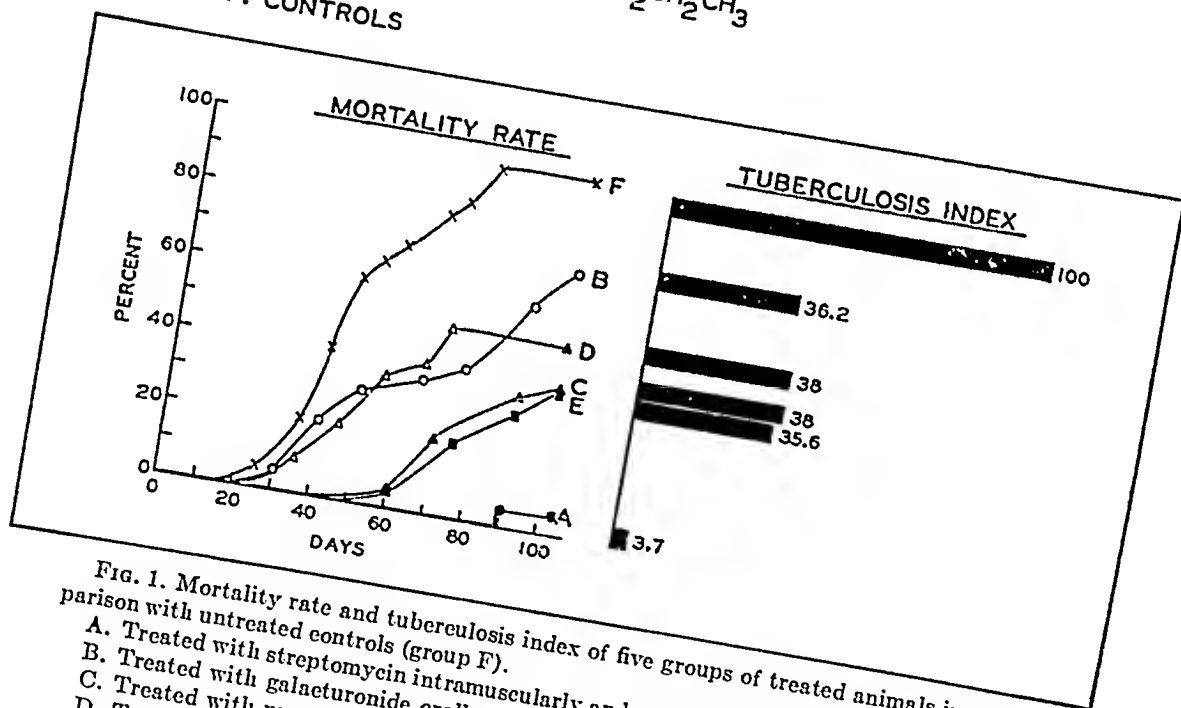
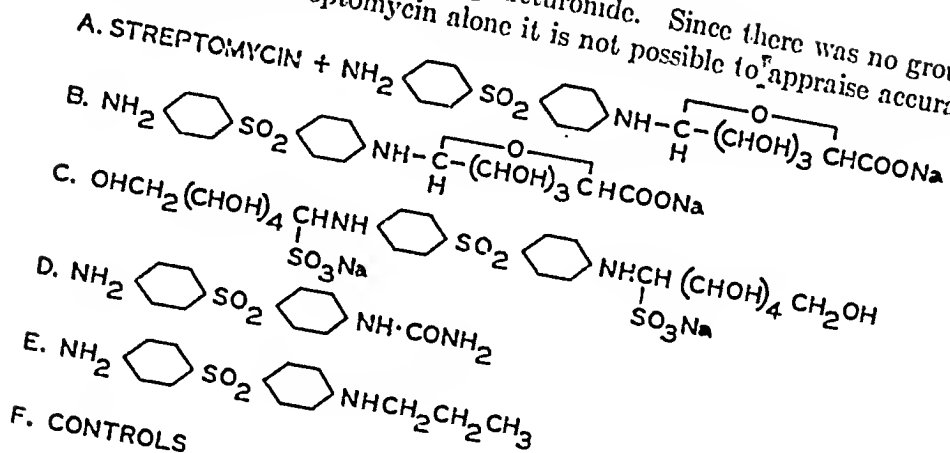


Fig. 1. Mortality rate and tuberculosis index of five groups of treated animals in comparison with untreated controls (group F).

- Treated with streptomycin intramuscularly and galaeturonide orally.
- Treated with galaeturonide orally.
- Treated with promin orally.
- Treated with carbamyl derivativ
- Treated with a n

the full value of the combined treatment. In this laboratory it is not believed that any of the above treatments have been achieving the full value of the combined treatment.

the full value of the combined treatment, but in the light of other experiences in this laboratory it is not believed that the effect obtained in group A could have been achieved with the antibiotic alone.

DISCUSSION

The present experiments undertaken with a view of testing several new sulfones in the hope of finding a safer and if possible a more effective compound than promin for application in the combined treatment with streptomycin have borne only partially fruitful results. On the basis of preliminary pharmacological studies with the monogalacturonyl derivative of diaminodiphenylsulfone in rats it appeared to offer advantages over promin because of its lower acute toxicity on intravenous injection, longer retention in the body, and a more favorable distribution in the tissues as between the liver and blood. However, on continued oral administration to guinea pigs, the procedure employed in the present chemotherapeutic tests, this compound actually proved to be more toxic than promin, probably by virtue of its better absorption, longer retention and greater cumulative effects. Nevertheless, the combined treatment with this compound and streptomycin resulted in a degree of protection against the disease in the experimental animals at least as great as from the application of streptomycin and promin in the previous study (4). Actually the results in the present study appear to indicate a higher degree of efficacy, since treatment was continued for only sixty-three days, and the animals were examined for evidence of tuberculosis after a six weeks' period of no treatment, whereas in the previous study treatment was continued with relatively smaller doses of streptomycin without interruption to the end of the experiment. Moreover, the infection in the present study was considerably more virulent as evidenced by 95 per cent mortality in the controls within seventy-five days as against 65 per cent mortality at 10 1days in the previous study.

The nearly uniformly positive response to tuberculin of the animals in group A, despite the low incidence of gross tuberculous infection and the minimal lesions found in the few, suggests that the allergy induced by the initial infection has not abated in the course of treatment, and perhaps also indicates that these animals may have acquired and have retained some degree of immunity. It would be interesting to study the response of such animals to reinfection with a standard dose of bacilli of standard virulence. That these animals were not sterilized by the treatment is evident from the fact that the subinoculation tests gave almost uniformly positive results.

The search for a better sulfone than promin has not been wholly fruitless. The n-propyl derivative of diaminodiphenylsulfone, used in group E, though no more effective than promin in reducing the extent of tuberculous involvement, as indicated from present and previous experiments (8, 9) is definitely less toxic than promin, this probably by virtue of its poor solubility and absorbability.

Because of its insolubility and low toxicity it has been impossible to obtain an LD₅₀ dose of the n-propyl derivative. A test on the comparative subacute and chronic toxicity of this compound and promin was carried out on guinea pigs. The compounds were administered in 1.0 g. per kg. doses twice daily to two groups of animals 10 each over a period of fifteen days. All the animals receiving promin developed cyanosis, hyperexcitability, tremors and flaccid

paralyses and died in three to five days. Reduction of hemoglobin and the appearance of methemoglobinemia were noted in all cases. The animals receiving the n-propyl compound showed no symptoms, no blood dyscrasias and gained weight normally. Blood level determinations made at various intervals from three to twenty hours following the last dose during the course of treatment showed a range of 40 to 85 mg. per cent in the promin animals and 3.4 to 4.8 mg. per cent in the n-propyl group. It may be concluded from this that the n-propyl derivative is less than one-fifth as toxic as promin and, while it is difficult to attain high blood levels with this drug, they seem to be sufficiently effective judging from the chemotherapeutic response. It seems quite clear, therefore, as previously pointed out (6), that mono-substituted alkyl derivatives of diaminodiphenylsulfone have an advantage over the mono- and di-substituted water-soluble derivatives by being equally or possibly more effective, less toxic and better retained in the body, even though their absorbability is poorer.

SUMMARY AND CONCLUSIONS

1. The chemotherapeutic efficacy of three mono-substituted derivatives of diaminodiphenylsulfone has been studied in experimental guinea pig tuberculosis in comparison with promin. The compounds were the monogalacturonyl derivative (I), the monocarbamyl derivative (II) and the mono-n-propyl derivative (III). The chemotherapeutic effectiveness of these compounds, expressed as the ratio between the extent of tuberculous involvement in the controls and treated animals was 2.7 for I, 2.6 for II and 2.8 for III, as compared with 2.6 for promin. The n-propyl derivative is less than one-fifth as toxic as promin.
2. The chemotherapeutic effectiveness in a group of animals treated with streptomycin and compound I was 27:0. Seventy-five per cent of the animals in this group showed no gross evidence of tuberculosis or only doubtful and insignificant lesions, though 95 per cent of them reacted to intracutaneous tuberculin, and subinoculation tests with tissue suspensions gave positive results in nearly all cases.
3. The combined application of streptomycin and the monogalacturonyl derivative of 4,4'-diaminodiphenylsulfone in the treatment of experimental tuberculosis gave as good results as those previously reported with streptomycin and promin.

SUMARIO Y CONCLUSIONES

1. En la tuberculosis experimental del cobayo estudióse la eficacia quimioterapéutica de tres derivados monosustitutivos de la diaminodifenilsulfona, comparándola con la de la promina. Trátase de los derivados monogalacturonílico (I), monocarbamílico (II) y mono-n-propílico. Expresada en forma de proporción entre la extensión de la invasión tuberculosa en los testigos y en los animales tratados, la eficacia quimioterapéutica de dichos compuestos representó 2.7 para el I, 2.6 para el II y 2.8 para el III, comparado con 2.6 para la promina. El derivado n-propílico resultó ser más de cinco veces menos tóxico que la promina.

2. En un grupo de animales tratados con estreptomycin y el compuesto I la eficacia terapéutica llegó a 27.0. Setenta y cinco por ciento de los animales de este grupo no revelaron signos macroscópicos de tuberculina administrada por vía subcutánea, y las pruebas de subinoculación verificadas con suspensiones de tejidos resultaron positivas en casi todos los casos.

3. La aplicación combinada de la estreptomycin y el derivado monogalacturonílico de la 4,4'-diaminodifenilsulfona dió en la tuberculosis experimental tan buenos resultados como los comunicados previamente con la estreptomycin y la promina.

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DIAGNOSTIC CULTURE OF TUBERCLE BACILLI

A Simplified Procedure in Public Health Work

MARJORIE VAN VRANKEN¹

Within the past few decades, diagnostic culture methods for determining the presence of mammalian tubercle bacilli in pathological materials have superseded animal inoculations which were preferred in diagnostic laboratories prior to this (1). Laborious and persistent trials of culture methods have led to the conviction that this important feature of the specific triad of tuberculosis diagnosis (2) should now be available universally in all public health laboratories and that simplicity and accuracy should be the criteria of the technique used in its performance (3). It is with this in mind that the following report is presented in the hope that it will not only aid others in the extension of public health facilities for this disease and in the ultimate welfare of the tuberculous patient.

In a routine testing for the presence of tubercle bacilli in a large number of sputum, urine and gastric specimens received in the Colorado Public Health Laboratories from various parts of the State, the method of procedure was to examine the specimens or concentrates from them by direct smear and Ziehl-Neelsen staining methods and, in addition, to perform an oxalic acid treatment (4) with Petraghani's medium and the Corper egg-yolk culture medium (5). Thus, 3,948 culture tests were performed from January, 1944 to December, 1945, with the result that 179 positive cultures were found which had been negative on direct smear. Of these 179, 5 became positive after an interval somewhere between six weeks' and six months' incubation at 37° C. The majority, 174, proved positive within a six weeks' incubation period. Unfortunately, the media used were not recorded in this series. These figures leave no doubt of the value of the culture method for disclosing tubercle bacilli in public health work.

In order to determine the comparative value of the two media, Petraghani's multiple mixture (3) and Corper's simple egg-yolk medium, the cultural findings were segregated on this basis since December, 1945, with the following results recorded in table 1.

It is noted from the findings recorded in table 1 that the positive cultures obtained with the use of an equal volume of 5 per cent oxalic acid at 37° C. for thirty minutes for destroying contaminants and planting on the egg-yolk medium (Corper) exceeded the positives on Petraghani's medium in a routine diagnostic culture test, 74 to 33. Both methods disagreed to some extent with each other in that a total of 87 positive results were obtained on either one or the other culture medium. The significance of this could be exaggerated if it were not known that routine clinical specimens may run irregularly at times so far as the distribution of small numbers of tubercle bacilli are concerned. The lack

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of homogeneity in clinical specimens so far as tubercle bacilli are concerned accounts also for the fact that the more tubes planted, the more positive cultures may accrue regardless of the medium used as a nutrient, provided the nutrient falls into the category of one of those efficiently supporting growth from small plantings. However, regardless of this, the findings with the egg medium are strikingly more favorable, which may possibly be explained by the better nutrient properties of the egg-yolk as compared with the Petraghani medium hampered by a retardant dye, malachite green, and multiple ingredients serving only as diluents for the good nutrient—the egg-yolk.

In the search for a more suitable reagent than sodium hydroxide, or one that would be adaptable to elaboration with the oxalic acid reagent, Corper and Stoner (6) studied trisodium phosphate, a crystalline, chemically pure and stable alkaline salt, for its effect upon mammalian tubercle bacilli. It was found that

TABLE 1

A comparison of cultures for tubercle bacilli in sputa using Petraghani's medium and the egg-yolk medium (Corper)*

SPUTA TESTED AND TOTAL POSITIVES	PETRAGHANI'S MEDIUM			EGG-YOLK MEDIUM			POSITIVE WITH BOTH MEDIA		
	Positive at 3 weeks	Positive at 6 weeks	Positive after 6 weeks	Positive at 3 weeks	Positive at 6 weeks	Positive after 6 weeks	Positive at 3 weeks	Positive at 6 weeks	Positive after 6 weeks
784 specimens yielded a total of 87 positives†	19	12	2	32	34	8	11	7	2
	Total 33			Total 74			Total 20		

* The oxalic acid preliminary treatment was used for all these sputa with neutralization with sodium hydroxide before planting.

† At least 3 tubes of culture medium were planted from each sputum on each medium used. Forty-two of the 87 positive cultures were negative by direct smear examination.

this reagent possessed a number of decided advantages for destroying contaminations in sputum, urine, gastric contents and pus in preparation for the cultivation of tubercle bacilli in clinical-pathological and public health work. The advantages were that a 23 per cent sodium phosphate ($\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$) solution in equal volume added to these specimens could remain in contact at room temperature for up to seven days without harm to the tubercle bacilli, and this amount and time sufficed in most cases to destroy all contaminants found in the usual pathological specimen. This enables the technician to prepare his material without rush and allows sufficient time to prevent the usual cautious watch period necessitated by all reagents previously described where neutralization had to be performed within one-half to two hours at least, frequently breaking up the day's continuity in laboratory work and necessitating continuous handling to consummation of the planting. In addition, if an oxalic acid preparation were forgotten and allowed to exceed the two-hour contact period without neutralization, the specimen, of which usually only one is available in

public health work, was lost; while in the sodium phosphate procedure, a day or two additional contact was not particularly detrimental to the tubercle bacilli. With a view, therefore, to comparing the new sodium phosphate procedure with the tried and reliable oxalic acid procedure previously chosen, the two reagents were tested on a consecutive series of 1,000 specimens (mostly sputa) received in the Colorado Department of Health Laboratories. All determinations for growth of tubercle bacilli were tested on the glycerol egg-yolk medium (Corper), which in our hands has proved to be the best nutrient for mammalian tubercle bacilli thus far described. The results of these tests are recorded in table 2. Although the figures recorded in table 2 are not exactly comparable because the 1,000 consecutive specimens were tested at different times by the two preliminary treatment methods, it is obvious that the trisodium phosphate method appears to yield a better percentage of positive cultures, 127 as compared with 108 per 1,000 specimens examined. Its value is significantly enhanced in the "positive culture-negative direct smear group" in which case twice as many

TABLE 2
Comparison of tubercle bacillus cultures on egg-yolk medium following the treatment of 1,000 specimens either with the sodium phosphate or the oxalic acid

METHOD OF TREATMENT	POSITIVE BY DIRECT SMEAR	CULTURES POSITIVE	POSITIVE CULTURE FROM DIRECT SMEAR NEGATIVE SPECIMENS	NEGATIVE CULTURES FROM DIRECT SMEAR POSITIVE SPECIMENS	CONTAMINATED OR LOST SPECIMENS
Oxalic acid.....	116	108	32	42	8
Sodium phosphate.....	113	127	64	35	13

positive results were obtained by the phosphate method used on routine single specimens.

In another analysis of the findings with routine health department specimens, the entire figures for the oxalic acid treated specimens were compared with those obtained when the phosphate treatment had been used to note the advantages in smear-negative specimens particularly. The oxalic acid treatment had been used from January, 1944 through December, 1945, on 3,948 specimens with the result that 179 positive cultures for tubercle bacilli were found in the absence of positive findings for acid-fast bacilli in the smears microscopically examined. From January, 1946 to September, 1946, 1,137 specimens were tested, using the phosphate treatment and planted on the egg-yolk medium with the result that 56 yielded positive cultures for tubercle bacilli in the absence of acid-fast bacilli in the smears examined microscopically. The relative findings for the same number were 179 for oxalic acid as compared with 194 for the phosphate. It is obvious that the trisodium phosphate reagent, an equal volume of 23 per cent ($\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$) added to sputum or similar specimens without acting destroying contaminants usually present in such specimens without acting detrimentally upon tubercle bacilli contained in those specimens. It is even

possible to consider placing the phosphate in the specimen bottle used for collecting and shipping the specimen, even though this has not been tried by us as yet, because at room temperature the trisodium phosphate in concentration used is without detrimental effect on the viable tubercle bacilli at room temperature for up to one week's contact. It can act as a retardant to the growth of contaminants in the specimen from the time of collection until delivered to the laboratory when a day of incubation at 37° C. will destroy the remaining viable contaminating microorganisms.

SUMMARY AND CONCLUSIONS

1. As a result of a test with routine specimens, it was found that the oxalic acid egg-yolk method devised by Corper and his colleagues for the diagnostic culture of tubercle bacilli from human pathological specimens (including sputum, urine, gastric washings, purulent fluids, etc.) is superior to the treatment with the oxalic acid reagent and culture on Petraghani's malachite green multiple mixture medium used in many health and sanatorium laboratories.

2. Trisodium phosphate ($\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$), used in equal volume of 23 per cent solution for twenty-four hours at 37° C., and studied and introduced originally by Corper and Stoner, has been found to be a superior reagent for destroying contaminating microorganisms in pathological specimens for the cultural diagnosis of tuberculosis. Combining the phosphate treatment with the egg-yolk medium (Corper) provides a simple diagnostic procedure to isolate human and bovine tubercle bacilli from routine specimens. It is recommended on the basis of extensive routine tests in public health work reported on here.

SUMARIO Y CONCLUSIONES

1. Como resultado de una prueba verificada con ejemplares corrientes se observó que la técnica de la yema de huevo y ácido oxálico, introducida por Corper y colegas, para el cultivo diagnóstico de bacilos tuberculosos procedentes de ejemplares patológicos humanos (incluso esputo, orina, lavados gástricos, líquidos purulentos, etc.) es superior al tratamiento con el reactivo de ácido oxálico y al cultivo en el medio múltiple de Petraghani a base de verde de malachita que utilizan en muchos laboratorios de higiene y sanatorios.

2. Utilizado en un volumen igual de solución al 23% durante 24 horas a 37°C., el fosfato trisódico ($\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$), estudiado e introducido primitivamente por Corper y Stoner, ha resultado superior como reactivo para destruir los microbios contaminantes en los ejemplares patológicos recibidos para el diagnóstico cultural de la tuberculosis. La combinación del tratamiento con fosfato con el medio de yema de huevo (Corper) ofrece un sencillo procedimiento diagnóstico para aislar los bacilos tuberculosos humanos y bovinos de los ejemplares corrientes, y recomiéndase para empleo a base de las muchas pruebas sistemáticas en obras sanitarias aquí descritas.

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REHABILITATION DIFFICULTIES¹

EZRA BRIDGE²

Rehabilitation is never easy, never finished, never perfect. Its problems have been with us always.

As physicians we feel the pressure of its presence and the responsibilities it lays upon us. We must see that nothing develops that will lessen the patient's physical health; we must know the significance of different personality traits; we must be familiar with mental mechanisms and motives. We must increase our ability to influence people and remain friends.

The aim of rehabilitation is to bring about the optimum adjustment of each patient in spite of the physical defects, mental deficiencies, emotional weaknesses and social shortcomings that he may have.

All this is most worthy, but its accomplishment is most difficult. Take, for instance, the story of our own development. To obtain a contented adjustment for ourselves, our parents spend a gigantic amount of time and energy trying to instill into our hearts and minds valuable concepts of those social practices that keep us out of the clutches of the law; next our sweethearts, mothers-in-law and children take over; and finally each one of us devotes hours, days and years to personal improvement. The result of these diverse and well meaning attempts is only rarely satisfactory. What is usually accomplished is well stated in these words: "Outwardly I appear well adjusted, but inwardly I still have my ups and downs."

The nature of man's inner self, his psychosomatic side, is one of the complicating factors. Psychosomatic medicine means giving careful consideration to the entire man, not only to his physical problems, but also to those in the intellectual, mental and spiritual spheres. In this it resembles rehabilitation. Much is heard about it these days; it is frequent in the literature, often thought of at the bedside and constantly whispered about in consultations.

This word "psychosomatic" comes from two Greek words, *Psyche* and *Soma*; words far apart in their origin. *Psyche* in Greek means butterfly and also soul. *Soma*, or body, recalls a savage, heady liquor. Little wonder that they make trouble for the rehabilitator with his aim of contented adjustment.

Putting these two influences side by side and expecting them to exist peacefully is asking for trouble. In some natures *Psyche* is the dominating influence, in others *Soma*; in all the battle between soul and body goes on. Take for instance George and his problem of adjustment to society. He came to us six years ago. He was a laborer. Social investigation showed he drank, hung around saloons and dives, begged from acquaintances as well as

¹ Presented at the Mississippi Valley Tuberculosis Conference, Chicago, Illinois, October 9, 1945.

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strangers. He contracted tuberculosis. We admitted him four times; he absconded an equal number. The fifth time he went AWOL, got drunk, landed in jail and finally returned to the hospital. To stop his craving for alcohol, we suggested investigating Alcoholics Anonymous. On being told what it was, he replied that drunk or sober he didn't care about being anonymous, that he was no shrinking violet. In due time we started rehabilitation.

We put him through psychological tests, made his psychograph, analyzed his personality, delved into his earlier education, inquired into his esoteric nature, searched for his latent capacities and determined his vocational proclivities. We found he was capable of no special skills and that his rehabilitation depended upon his losing his taste for alcohol. Finally we put him to work for a few hours a day as janitor's helper; came pay-day and \$12 was his. Promptly he disappeared only to return in a disheveled condition three days later. Asked what happened, he replied, "Doc, I just can't stand prosperity."

Our educational efforts have so far brought a partial adjustment. George has learned something of the problem of taking care of his health. He is more cognizant of good social usage, but cancellation of his court commitment is not yet feasible. His Psyche and Soma are living more peacefully together. But there is more work to be done. He must be interested in broader pursuits and stimulated intellectually. If he is let out now he will probably seek his old haunts. As long as the desire for alcohol remains he is not completely rehabilitated.

Another difficulty in rehabilitation arises from the bisexual character of our natures. Each man has non-genital characteristics belonging to woman and no woman is entirely free from certain male markings and thought patterns. This mixture has been called the mosaic of androgyny (andro-male; gynec-female). The term does not imply a lack of the primary sexual function, but complicates life for the individual by influencing his emotional, physical and social reactions.

Take the problem in emotional adjustment in Elizabeth, whom we have known since 1941. As part of the admission technique, her atavistic, parental, educational and religious backgrounds were studied. Tests by psychologists, teachers, vocational director and physicians added data. She had a sheltered girlhood. Early in life she married a man who lavished care and attention on her. Then one day he dropped dead.

After his sudden death she became a different person. Her male personality traits came to the front. Wherein before she was quietly receptive, now she was domineering, managing, tyrannical; instead of handling home affairs she walked the streets and promptly got herself into trouble. It was at this time she was found to have tuberculosis. Examination disclosed a strong, sturdy woman with shoulders broader and hips narrower than expected. Her extremities have masculine contours and her hair distribution resembles that of a male. As she improved physically a rehabilitation program was started. But to make any plan appeal to her for long was impossible. Her restlessness continued unabated. On one occasion she spirited two weak-minded women away from the hospital. Police located them in a cheap rooming house in an unimproved part of town.

REHABILITATION DIFFICULTIES

But this was not allowed to discourage us. The ramifications of her health problem and her emotional and social responsibilities were again explained to her. New approaches were tried, but so far to no avail. She remains an uncontented soul, full of contradictory attitudes and actions. She illustrates well the slogan: "If the learner has not learned, the teacher has not taught."

The third case shows the difficulty in making a medical school graduate conscious of some of his problems.

John was an interne when he developed tuberculosis. His scholastic record had always been high. At the hospital he was dependable, quick to accomplish the daily tasks, pleasant with patients and associates. While under treatment with us all phases of his problems were discussed with him and, when well on the road to recovery, he was allowed to attend staff conferences where he heard repeated admonitions to patients being discharged. Finally he was given an arrested classification and a maximum sanatorium benefit discharge. He returned to part-time hospital work with our blessing.

It was not long before he was forgetting what he had been told about his health hazard. He stayed overtime on the wards, met all emergencies and accepted new responsibilities. Repeatedly we cautioned him to observe more rest and to take it easy. But, no! Now he is back in bed with an open lesion, another case to be chalked against the teacher because the learner did not learn. This propensity not to hear or appreciate what the other fellow says, is deep seated.

However, in spite of the many difficulties, rehabilitation is a beneficent development in our sanatoria. It puts new life into the staff; leads to a broader outlook; makes everyone brush up on principles and brings an inner glow to all identified with the work. The patients have more to live for and are encouraged by the renewed attention to their welfare.

But the difficulties besetting the way of the rehabilitator make the successful termination of many cases a long drawn out process.

MORTALITY STATISTICS FOR 1945

Fewer deaths occurred in the United States in 1945 than in either of the two preceding war years, according to figures released to-day by the U. S. Public Health Service. A total of 1,401,719 deaths were reported in the United States in 1945, as compared with 1,411,338 in 1944, 1,459,544 in 1943 and 1,385,187 in 1942.

In the first ten months of 1946 there were an estimated 1,162,000 deaths in the United States, as compared with 1,144,273 in the first ten months of 1945. All figures are for the continental United States and exclude deaths among the armed forces overseas.

Deaths from the major infectious diseases declined to new lows in 1945. The year set a record low for pneumonia and influenza. The total of 68,386 deaths from these respiratory causes was 8.2 per cent less than the previous minimum of 74,532 deaths in 1942 and 16.4 per cent less than the number reported for 1944.

Tuberculosis continued its decline in 1945. There were 52,916 deaths from this cause in the United States in 1945, 3.3 per cent less than the number in 1944 and fewer than in any previous year.

The ten leading causes of death in the United States are listed in table 1.

TABLE 1
Ten leading causes of death: United States, 1944 and 1945

CAUSE OF DEATH	NUMBER OF DEATHS		PER CENT OF ALL CAUSES	
	1945	1944	1945	1944
All causes.....	1,401,719	1,411,338	100.00	100.00
1. Diseases of the heart.....	424,328	418,062	30.3	29.6
2. Cancer and other malignant tumors.....	177,464	171,171	12.7	12.1
3. Intracranial lesions of vascular origin.....	129,144	124,250	9.2	8.8
4. Nephritis.....	88,078	91,687	6.3	6.5
5. Pneumonia (all forms) and influenza.....	68,386	81,804	4.9	5.8
6. Accidents excluding motor-vehicle accidents.....	67,842	70,955	4.8	5.0
7. Tuberculosis (all forms).....	52,916	54,731	3.8	3.9
8. Diabetes mellitus.....	35,160	34,948	2.5	2.5
9. Premature birth.....	31,614	33,120	2.3	2.3
10. Motor-vehicle accidents.....	28,076	24,282	2.0	1.7

[From a press release of the United States
Public Health Service, dated December 27, 1946]

AMERICAN TRUDEAU SOCIETY

Postgraduate Course in Thoracic Diseases

University of Colorado Medical School, Denver, Colorado

July 28 to August 9, 1947

A Postgraduate Course in Thoracic Diseases will be given at the University of Colorado Medical School from July 28 through August 9, 1947. Dr. H. Dumont Clark says: "The first week will be devoted to anatomy, surgical anatomy, physiology, pathological physiology, anesthesia, and certain treatment techniques including oxygen therapy, aerosol therapy, and lung immobilization. Much of this work will be in the form of demonstrations in the laboratories of the University of Colorado Medical School. Various operative procedures are to be demonstrated on the cadaver. Remainder of the first week and all of the second week are to be devoted to a consideration of various thoracic diseases with emphasis on tuberculosis. Contributions of psychiatry and rehabilitation programs to tuberculosis control will be included. The pathological lesions of the various thoracic diseases will be obtained from the extensive collection at Fitzsimons General Hospital and will be shown by a new micro-projector recently obtained by the University of Colorado Medical School. . . . It may be possible for us to house the students in one of the medical fraternity buildings near the school. Reservations will be made at nearby mountain resorts so that families of students and instructors can stay there if desired."

Tuition for this two-week course will be \$100.00. While it is planned primarily for physicians resident in the states of: Colorado, North Dakota, South Dakota, Nebraska, Kansas, New Mexico, Arizona, Utah, Wyoming, and Montana, undoubtedly some of those applying from other states will be accepted.

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VOLUME LV

Lobar and Segmental Collapse of Lung.—The paper is intended to present certain signs which are of value in the recognition of collapse of an entire lung or a major part thereof. Reviewing 85,000 chest examinations, 12,000 were reviewed in detail, 600 of whom had at least one lobe that was less than two-thirds its normal size. Only collapse due to intrinsic lung disease was included. The collapse was limited to a single lobe or segment in 71 per cent, involved 2 or more lobes in 18 per cent and was massive in 11 per cent. The left lower lobe was most frequently involved, the right middle and right upper being next in frequency. There would have been a larger number with extensive collapse if those following operative procedures had been included. The collapse of an entire lung, acute or chronic, usually reveals the characteristic X-ray signs of abnormal increased density, elevation of the diaphragm, displacement of the mediastinum and narrowing of the rib spaces. In acute collapse the increased density is usually homogeneous and the structure of the involved lung is obscured. The side of the chest containing the collapsed lung is more radiopaque as compared to the opposite side. The amount of displacement of the mediastinum is approximately the same regardless of which side is involved, and there is a definite inspiratory shift to the side of the lesion seen during fluoroscopy. The diaphragm is not only elevated, but usually shows some limitation of motion during fluoroscopy. The right side is more difficult to localize with a basal collapse. If it is remembered that most of these signs are the results of a decrease

in size of the involved lung, there will be less confusion with other disease processes. In chronic collapse of the lung there may be little difference from that of an acute collapse, or the area may be so small as to be difficult to discover. However, the collapsed lung lies posteriorly and medially and on the left is often partially obscured by the cardiac shadow or other mediastinal contents. On the right it blends with the shadow of liver, diaphragm and mediastinum. Here, too, there is a shift of the mediastinum although it is not so apparent. The uninvolved emphysematous lung tends to herniate through the mediastinum, usually in the anterior mediastinum. Pulmonary herniation is recognized chiefly in the lateral roentgenogram which shows an increase in the distance between the sternum and anterior border of the heart and ascending aorta. The distribution and size of the vascular shadows may also aid in the recognition of herniation. The size of the hernia depends upon the extent and duration of the collapse and in some it is so severe that the uninvolved lung may almost completely aerate the opposite chest. The right lung is most frequently and extensively involved. A sizable hernia was not observed in acute collapse in this series. Diaphragmatic changes are less marked in chronic collapse because of compensation by the herniated lung. This latter factor may also effect the apparent narrowing of rib spaces, but the tendency for the involved side to be smaller than normal is true in chronic as well as acute collapse.—*The Roentgen Appearance of Lobar and Segmental Collapse of the Lung: III.*

Collapse of an Entire Lung or the Major Part Thereof, L. L. Robbins & C. H. Hale, *Radiology*, July, 1945, 45: 23.—(G. F. Mitchell)

Collapse of Right Middle Lobe.—Collapse of the right middle lobe of the lung occurs frequently. In 600 cases of collapse studied, 26 per cent revealed collapse of the right middle lobe. It often is confused with interlobar effusion because in collapse of this lobe the septa tend to become closer together and the final shadow of increased density may thus simulate an effusion. However, if certain definite characteristics are looked for and their importance recognized, the diagnosis of collapse of the middle lobe can be accurately made. The middle lobe lies in the antero-inferior portion of the right chest making up essentially all of the pulmonary tissue adjoining the right cardiac border. It is demarcated by two septa, the minor, running more or less horizontally and the major running downward and anteriorly. The right middle lobe bronchus divides immediately into an antero-medial and postero-lateral branch. Complete obstruction of the right middle lobe bronchus results in marked decrease in the size of the lobe and roentgenologically forms somewhat of a pyramid with its base against the right heart border. That the lobe is the site of disease may not become apparent until some abnormality, such as loss of definition of the right heart border, occurs. Any interference with its aeration will produce this. The large space occupied by the lower lobe may give fairly good detail of the lower lung field, even in the presence of collapse of the middle lobe. In such a condition the lateral view is the most important factor in the examination. In this projection the middle lobe, when collapsed, appears as a band of increased density, 2 or 3 cm. thick located in the place of the antero-inferior portion of the major septum, the widest part lying against the anterior chest wall or diaphragm. It may be differentiated from interlobar effusion by this shape, for that of the latter is ovoid or elliptical and portions of the septa will usually be seen in their normal position.

The definition of the shadow of a collapsed middle lobe can usually be increased by the lordotic projection and can readily be seen by fluoroscopy. The hilum is seldom depressed as the result of the collapse of the middle lobe. Segmental collapse was seen more frequently than complete collapse, the antero-medial segment being more frequently involved. Only by careful observation of septa, shape and location can this type of collapse be recognized. In the anteroposterior X-ray film this shadow lies in direct apposition to the right heart border and does not extend laterally as far as the entire lobe, but in collapse of the postero-lateral segment, the right heart border remains sharply defined. Collapse of the middle lobe associated with collapse of the lower lobe may be difficult to identify. However, here the minor septum is impossible to demonstrate. In general, what has been said of the right middle lobe applies to collapse of the lingula on the left. The lingular bronchus arises from the proximal portion of the left upper lobe and divides into an antero-lateral and postero-medial segment. Bronchiectasis often produces collapse of the lingular associated with a similar involvement in the lower lobe, but it is not readily recognized without bronchography. Collapse of the antero-lateral segment does not obliterate the left border of the heart. In the lateral projection it lies against the septum. A few cases of collapse of the postero-medial segment have been seen.—*The Roentgen Appearance of Lobar and Segmental Collapse of the Lung*: V. *Collapse of the Right Middle Lobe*, L. L. Robbins & C. H. Hale, *Radiology*, September, 1945, 45: 260.—(G. F. Mitchell)

Segmental Collapse of Lung.—Collapse of a single lobe of the lung is most frequently misinterpreted when it occurs in one of the upper lobes and is confused with a localized area of consolidation, a mediastinal tumor, an aortic aneurysm or, in some instances, is completely overlooked. In the group of 600 cases forming the basis of the study, the upper lobes were involved in 16 per cent. Certain roentgenological signs will, if recognized,

lessen some of the confusion regarding its diagnosis and are described. The routine postero-anterior X-ray film is depended upon to show any areas of increased density, the presence and degree of emphysema of adjoining lobes, the position of the trachea and upper mediastinum, the relative planes in which the hila are located and the minor septum. With a few exceptions, the roentgen appearance of collapse of an upper lobe or of its segments is essentially the same regardless of the side involved. The similarity in appearance of a right middle lobe and a lingula on the left has been mentioned. The lingula is often collapsed when the remainder of the left upper lobe is involved, but in none of the cases studied was collapse of a middle lobe associated with a similar process in the right upper lobe, unless the entire lung was collapsed. Therefore, the presence of the lingula is significant only when it and the remainder of the left upper lobe are simultaneously collapsed. When this occurs, the entire shadow of increased density is slightly larger than that of collapse of the right upper lobe and extends farther inferiorly along the anterior chest wall. Evidence in the lateral film that a major septum is no longer in its normal position may be the first evidence suggestive of decrease in the size of an upper lobe. The septum will lie farther anteriorly, and its superior portion will extend higher in the chest. It may also be noted that the normal pulmonary markings appear to be more closely grouped than usual. As collapse increases the lung markings seem to be crowded together and finally the increased number of markings per unit area will make the smaller lobe cast a definite shadow of increased density in contrast with the uninvolved lung. This shadow of increased density has a rather typical shape and position, being somewhat fan-shaped or triangular with a fairly broad base as it first becomes visible. Later the peripheral border becomes shorter, the apex of the shadow appears to arise from the top of the hilum, and its base extends against the top and antero-medial surface of the chest wall. This shape is seen in both antero-posterior and lateral films. A collapsed upper lobe may become so small and move so far

anteriorly and medially that the shadow of increased density may blend with that of the upper mediastinum, the combined shadow merely suggesting mediastinal widening, or in the lateral view it may become assimilated with that of the upper anterior chest wall obscuring the area between the ascending and transverse portions of the aorta and chest wall. Nevertheless, the area of increased density can be seen in this view if it is determined whether the ascending and transverse aorta are as distinctly outlined as usual. The appearance of the ascending aorta is of especial importance in relation to the right upper lobe. In collapse of a left upper lobe, the transverse portion of the arch of the aorta may not be clearly defined. An entirely collapsed left upper lobe seldom becomes as small as that of a right upper lobe. A decrease in size of an upper lobe may be interpreted as showing a minimal tuberculous lesion because the area of collapse is small and the decrease in the size of the lobe is not appreciated. If collapse is due to a chronic condition in which secondary fibrosis occurs, such as tuberculosis or bronchiectasis, the process may remain stationary for many years. Acute obstruction occurs more rapidly and clears more rapidly. With decrease in size of an upper lobe the hilum is drawn to a higher level, and its superior portion may be merged in the shadow of increased density. As a rule, the greater the collapse the higher the level of the hilum though occasionally the presence of a tumor prevents the elevation of the hilum. The upper mediastinum and trachea may show some displacement toward the collapsed side, but this displacement is not as marked as in collapse of a lower lobe and, as a rule, the heart and lower mediastinum remain in their normal position. There may be some elevation and limitation of motion of the diaphragm, though a neoplasm in the upper lobe may produce phrenic nerve paralysis as an early manifestation. Any change in the position or contour of the septa may be of diagnostic importance. Except for the lingula, the segments of the upper lobes are divided into the apical portion, the antero-inferior portion, the postero-superior and the

lateral or axillary portion. Each of these is supplied by a branch from the upper lobe bronchus except the axillary segment which is supplied by two bronchi, usually branches of the bronchus to the postero-superior and antero-inferior segments. Any one of these segments may be collapsed singly. Collapse of the axillary segment is usually associated with collapse of either the antero-inferior or postero-superior portions or both. Segmental collapse of an upper lobe produces varying degrees of elevation of the hilum, the elevation being greater when the apical segment is involved, and an anterior shift of the major septum, the amount being dependent upon the degree of collapse and the segment involved. In some cases there is only accentuation of the anterior convexity of the septum. A collapsed segment does not produce marked displacement of the trachea and superior mediastinal structures, though such displacement may be considerable with a collapsed apical segment, nor does it produce much change in the position or motion of the diaphragm. Emphysema in adjacent pulmonary tissue is not striking.—*Röntgen Appearance of Lobar and Segmental Collapse of the Lung: VI. Collapse of the Upper Lobes*, L. L. Robbins & C. H. Hale, *Radiology*, October, 1945, 45: 347.—(G. F. Mitchell)

Experimental Pulmonary Collapse.—Current methods of maintaining collapse in extrapleural pneumothorax are not satisfactory. An ideal compressing substance should fulfill the following requirements: (1) non-irritating and one which would permit body fluids to organize, forming a permanent fibrous pack, (2) non-carcinogenic and non-antigenic, (3) light in weight and incapable of perforating the pleura and lung, (4) insoluble, (5) offering little resistance to X-rays and (6) capable of being molded. Various substances were tried with unsatisfactory results. Methyl methacrylate, better known as lucite, was first used in dental prosthesis. Implants were introduced into the pleural cavity of 30 adult rats. Except for small effusions and slight dyspnea, there were no abnormal reactions. The rats were killed after ten days to eight months. Necropsies showed varying degrees of atelectasis. In a few, pneumonia was found, and there was empyema in 2. Pleural reaction was minimal. In 18 animals there was fluid in varying stages of organization. In 10, the implants remained free in the pleural cavity. Extrapleural collapse was affected in 10 healthy dogs. The spaces were filled with solid balls of lucite. In 8 animals, sero-sanguineous exudates appeared in forty-eight to seventy-two hours. There were no deaths. Necropsies showed localized atelectasis in the lung adjacent to the space. The lucite balls were found to be fixed in dense masses of hyaline connective tissue. Extrapleural pneumothorax, using lucite, was carried out in 8 tuberculous patients, with gratifying results.—*Experimental Surgical Pulmonary Collapse*, D. A. Wilson & H. Baker, *Surg., Gynec. & Obst.*, June, 1946, 82: 735.—(A. G. Cohen)

Atelectasis.—The immediate cause of post-operative pulmonary atelectasis is a plug of mucus or fibrin which seals one of the larger or smaller bronchi. Air in the alveoli distal to the plug is absorbed and collapse occurs. In treatment, the important thing is removal of the plug. Bronchoscopy can, of course, be done but it is not always necessary to employ this procedure in a sick postoperative patient. The author has frequently found simpler measures successful. Occasionally a slap on the back, encouraging a hard coughing spell, or posturing the patient will dislodge a bronchial plug. When these fail, other measures are available and are based on the following four factors which must be corrected: (1) dryness of the plug, partially caused by pre-operative atropine; (2) bronchospasm; (3) gravity or position of the patient—most plugs occur in dependent portions of the lungs; (4) relative pressures in the bronchial tree; when pulmonary collapse occurs, intrabronchial pressure and pressure from surrounding structures will tend to drive the plug in deeper. An attempt can be made to remedy each of these four factors. Any good expectorant, such as the iodides, will aid in liquefying and floating the plug. Bron-

chospasm can be relieved by ephedrine or adrenalin. Gravity can be utilized to aid in expulsion of the plug by posturing the patient and encouraging him to cough ten to twenty minutes after the bronchodilator is administered. The posturing should be repeated every hour, the expectorant and bronchodilator every four hours. If no relief is obtained after twenty-four hours, bronchoscopic aspiration can be done. There is no risk in delaying bronchoscopy for this length of time provided the possibility of lung suppuration can be minimized. Adequate prophylactic doses of sulfadiazine should be given. Since the above procedures were adopted, bronchoscopy has not been necessary in any of the cases occurring at the Montreal Military Hospital. Six illustrative case reports are cited.—*The Medical Treatment of Postoperative Pulmonary Atelectasis*, M. Aronovitch, *Canad. M. A. J.*, September, 1945, 53: 222.—(H. R. Nayer)

Bronchial Aspiration in Atelectasis.—Atelectasis caused by obstruction of a bronchus, may produce an abscess, bronchiectasis or bronchopneumonia. Six hours after total obstruction of a bronchus, a hyperemic apneumotosis starts in the lung tissue depending on the obstructing bronchus. Blood penetrates into the alveoli. This condition is fairly common as postoperative complication and then often is interpreted as pulmonary congestion, cortical pleurisy or bronchopneumonia. The onset is ten to twenty-four hours after abdominal surgery. After thoracoplasty, it develops more rapidly, within six to eight hours. The predominant sign is dyspnea. Aspiration of the bronchus is indicated and done through a bronchoscope. It is not necessary to aspirate a great quantity of secretion. A small amount of viscous material when adherent to the bronchial wall will completely obstruct the feeding bronchus of a lobe. Sometimes a real tamponade obstructing the larger bronchi may occur. It is generally enough to relieve the obstruction in the large bronchus to obtain a complete evacuation of the secretions in the atelectatic part of the lung. The earlier the bronchial aspi-

ration takes place the greater the chance that only a small amount of secretion has formed and that one aspiration will be sufficient to relieve the symptoms. Postural drainage, maintenance of the cough reflex and atropine are helpful. The author has done forty-one aspirations in 23 patients. One patient needed five, 4 needed three, 6 needed two and 12 needed only one aspiration. Absolute indication for bronchial aspiration is postoperative atelectasis, although a great number of cases clear up spontaneously. No benefit would be obtained if bronchopneumonia has already set in. In none of the cases has the author seen any complications. The aspiration was followed by immediate relief of all the symptoms as proved by fall of temperature and X-ray evidence.—*Broncho-aspiracion en la atelectasis post-operatoria (con especial referencia a los operados de toracoplastia)*, A. E. Bence, *An. Cated. de pat. y clin. tuberc.*, December, 1944, 6: 302.—(W. Swienty)

Postoperative Pulmonary Collapse.—The most important aspect of this serious complication is its prevention. Analysis of 2,704 consecutive cases showed that drop ether anesthesia gave the highest number of respiratory complications, and any method of anesthesia that used ether showed the same tendency. With proper premedication, cyclopropane anesthesia gave rise to very few respiratory complications and none of them were of a serious nature. The author feels that preoperative and postoperative orders, as regards to sedation, should be given by the anesthesia department, and thus complications can be avoided. Premedication should be sparing. In general the author prescribes less morphine than is in current use, rarely exceeding $\frac{1}{6}$ to $\frac{1}{16}$ grain. Atropine or hyoscine, as the case may be, are to be given about forty-five minutes before the operation. To reduce the interval is to invite trouble because the maximum anhydrotic effect of these drugs would then be reached when the patient is already receiving inhalation anesthesia. This would cause the secretions which were present in the bronchial tree to become inspissated. It was found

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that heavy smokers and patients with oral sepsis have the highest incidence of pulmonary complications. When atelectasis or massive collapse does develop, an effective treatment consists of applying a cotton sponge soaked in 10 per cent cocaine and epinephrine solution to the pyriform sinus with a curved applicator. The effect is an immediate stimulation of the cough reflex by the epinephrine, and an antispasmodic action of the cocaine, permitting large plugs of mucus, or quantities of pus to be coughed up freely. Relief is often instantaneous. Other therapeutic measures in prevention of collapse are frequent turning of the postoperative patient and encouragement of cough, inhalation of carbon dioxide and oxygen mixtures at regular hourly intervals, and administration of chemotherapeutic agents to prevent infection in the collapsed lung.—*A New Treatment for Postoperative Pulmonary Collapse*, E. H. Grandstaff, *Arch Surg.*, November-December, 1945, 51: 237.—(H. Marcus)

Pulmonary Complications in Burns.—Large volumes of plasma and other fluids were used in the treatment of the victims of the Coconut-Grove fire. Fluids were given to patients with shock or with signs of imminent shock. Ninety-eight patients received an average of 1,850 cc. of plasma. Seventy-four patients received an average of 2 liters of saline solution intravenously in addition to plasma during the first twenty-four hours after the fire. In addition, various fluids were given orally. The amount of fluid given was related to the extent of the surface burns. The severity of the respiratory lesions was also usually related to the extent of the burns. On the basis of the observations the conclusion is made that "it appeared that pulmonary edema did not occur and that the respiratory complications, in general, were not aggravated as a result of this therapy as it was carried out in these cases." The symptoms, roentgenological and pathological findings were consistent with severe laryngo-tracheobronchitis with obstruction of the air passages. The cause of the pulmonary lesions was not determined. The possibility of a pulmonary irritant such as phosgene, or of the ordinary

gases and fumes resulting from incomplete combustion is discussed.—*Effects of Plasma and Fluid on Pulmonary Complications in Burned Patients: Study of the Effects in the Victims of the Coconut Grove Fire*, M. Finland, C. S. Davidson & S. M. Levenson, *Arch. Int. Med.*, May, 1946, 77: 477.—(G. C. Leiner)

Pulmonary Lesions in Burns.—The victims of the Boston Coconut Grove fire died either of extensive burns or of respiratory tract injuries. Inhalation of the hot fumes produced a laryngo-tracheobronchitis with corresponding clinical and roentgenological effects. Atelectasis, emphysema, miliary mottling, pulmonary edema and infarcts were the roentgenological lesions encountered. Atelectasis usually appeared in the form of triangular, bandlike or fine linear areas of increased density, located anywhere in the lung fields; extensive changes were associated with compensatory emphysema, elevation of the diaphragm or displacement and contraction of the hilar shadows. Lobar atelectasis was rare. Emphysema was best seen in expiratory films and was usually coexistent with atelectasis. The miliary mottling observed in a few cases was thought to be due to numerous small areas of atelectasis. Pulmonary edema and infarcts were rare findings. Both roentgenologically and at autopsy. Generally speaking, there was a fairly close correlation between the severity of the clinical condition and the extent of the X-ray findings. In most patients, the greater portion of the pulmonary lesions cleared up by the end of the first week; patients who had adequate follow-up examinations showed no abnormalities six months to two years after the disaster.—*Roentgenologic Findings in the Lungs of Victims of the Coconut Grove Disaster*, M. Finland, M. Ritvo, C. S. Davidson & S. M. Levenson, *Am. J. Roentgenol.*, January, 1946, 55: 1.—(P. Lowy)

Treatment of Pulmonary Embolism.—The intravenous administration of morphine and papaverine has been found to give the best results in mild or moderately severe pulmonary embolization. Disregarding the few

cases of severe embolization which may have been saved by a Trendelenburg operation, one has to admit that effective therapy for this condition is entirely lacking. In the author's hands, good results have been obtained in moderately severe and severe cases by the immediate administration of between 5 and 50 cc. of $\frac{1}{2}$ per cent solution of novocaine intrapleurally. Pain in the chest, and inability to take a deep breath, or to breathe at all on account of pain, are very prominent symptoms in pulmonary embolism. This condition is immediately and dramatically remedied by the injection of novocaine. Although it is not entirely clear in just what fashion the injection of novocaine strengthens the circulation and the failing right heart, it seems probable that the abolition of pain sets in motion a train of reflexes which remedy the fundamental circulatory difficulties of such patients. The results are most pronounced in patients with bland thrombosis and normal hearts. However, even in septic thrombosis complications can probably be cut down by prompt administration of treatment, and cardiac patients are also decidedly benefited.—*Die Behandlung der Lungenembolie mittels örtlicher Betäubung, K. Lange, Schweiz. med. Wchnschr., January 26, 1946, 76: 65.*—(H. Marcus)

Pulmonary Embolism.—Pulmonary embolism is more often seen in the Northern clinics. Its incidence is highest during the cold season. In 95 per cent of all cases of pulmonary embolism the source of the embolus can be found in the deep veins of the legs. The incidence of fatal embolism is about one in 800 surgical patients. The earlier the diagnosis of phlebothrombosis and thrombophlebitis is made the earlier the bilateral vein interruption is done the shorter is the period of disability. Femoral vein interruption should not be performed in the treatment of true thrombophlebitis after the seventh day of the disease. The older the patient the greater the likelihood of fatal embolism complicating illness or surgery. For this reason prophylactic femoral vein interruptions have been carried out in the aged

in 34 patients. Concomitant femoral vein interruption has been advocated in low thigh amputation. In the cardiac patient femoral vein interruption should be done if infarct occurs, if there are any signs of thrombosis in the leg veins and possibly prophylactically. Prophylactic femoral vein interruption should be considered in elderly patients with fracture of the hip and in those requiring prostatectomy. Early ambulation in postoperative patients may reduce the incidence of thrombosis in the legs. Heparin is useful if repeated minor infarcts have occurred after femoral vein interruption. At the present time, dicumarol treatment is not as safe or as innocuous a procedure as femoral vein interruption. Femoral vein interruption was carried out in 464 patients. In 367 patients satisfactory follow-up reports were obtained. There was no fatal complication. Wound infections occurred in 5 patients, lymphorrhea in 15 patients. Bilateral femoral vein interruption is recommended routinely if either side is done. The ideal site for the interruption is the superficial femoral vein just below the profunda femoris. Following the interruption only 5 per cent of the patients have had infarcts of any degree. These infarcts may have come from the iliac region. The operative technique is described in detail.—*Venous Thrombosis and Pulmonary Embolism: Further Experience with Thrombectomy and Femoral Vein Interruption, A. W. Allen, R. L. Linton & G. A. Donaldson, J. A. M. A., June 9, 1945, 128: 397.*—(H. Abeles)

Pulmonary Embolism.—The emboli that occlude the pulmonary arteries arise most frequently in the systemic veins; rarely, an embolism may come from the right side of the heart. Pooling and coagulation of the blood in the deep veins of the leg are the essential factors in 99 per cent of the cases of pulmonary embolism. The septic form of thrombophlebitis rarely results in embolism. Slowing of the venous return from the lower limbs, changes in the blood such as anemia and a rapid clot retraction time, and trauma, such as childbirth and abdominal operations, favor

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thrombosis in the lower extremities. However, thrombosis may occur in apparently healthy and active individuals. The classical symptoms and signs of pulmonary embolism are chest pain, bloody sputum, signs of pleuritis and consolidation, dyspnea and cyanosis. More frequently, the physician is confronted with the signs of shock. Chest pain with typical anginal radiation is not uncommon. In the case of small emboli, the only symptoms may be weakness, tachycardia and slight fever; in such cases, abnormal physical signs or X-ray findings may be absent. When a large embolus blocks the pulmonary artery, acute cor pulmonale will supervene. Pulmonary embolism occurs most frequently without visible evidence of thrombophlebitis. Pain four or five inches above the Achilles tendon, on dorsiflexion of the foot, as described by Homans, is a valuable sign in recognition of silent thrombophlebitis. Various changes in the electrocardiogram have been noted. Typical changes have been described in severe complexes have been described in severe episodes. A normal tracing is often present in minor episodes. The prognosis is extremely difficult to determine. Treatment falls under three headings: (1) prevention of embolism in patients on bed-rest; an attempt should be made to combat the factors which increase coagulability of the blood by controlling dehydration and anemia; patients should be gotten out of bed as soon as possible; massage and active and passive motion of the lower extremities are valuable in speeding up venous flow; (2) treatment where one embolism or thrombophlebitis has occurred: venous ligation and anticoagulants are the most valuable measures, but each must be used with due regard to the individual patient; dicumarol is the most convenient anticoagulant but its effect must be followed with daily prothrombin time determinations; this drug is contraindicated in purpura, existing prothrombin deficiency as in liver disease, subacute bacterial endocarditis, and renal insufficiency; (3) in the major attacks various drugs, particularly papaverine and morphine, are valuable in providing relief from symptoms. Oxygen to relieve cyanosis and phlebotomy to reduce marked venous distention are also useful.

—*Pulmonary Embolism*, N. Feeney, *Canad. M. A. J.*, August, 1945, 53: 132.—(H. R. Nayer)

Pulmonary Infarcts.—The roentgen diagnosis of pulmonary infarct is frequently missed. The error is almost always a "negative" one in that it is not suspected. It may mimic almost any other lung disease. This paper is partially based on 344 instances of aseptic hemorrhagic infarction seen during a ten-year period. In 174, infarction was the major cause of death, but in only 22 per cent was the correct diagnosis made. In recent years the differentiation from the pneumonias is important because of the use of sulfa drugs. The first papers on this subject appeared in 1922. Kirklin and Faust in 1930 stated: "It is difficult and at times impossible to make a diagnosis of pulmonary infarction from the roentgenogram. With the clinical data, however, the nature of the shadows appearing on the film may usually be accurately determined." As evidence has accumulated over a period of years, the varied appearances which an infarct may assume have become more generally understood. In most instances it is possible to suspect its presence from the roentgenogram alone. Clinical findings usually include hemoptysis with sudden sharp pleural pain, dyspnea, râles and changes in the character of the breath sounds. If a peripheral pleural surface is involved a friction rub may be heard. Physical findings vary with the position and age of the infarct. There is a moderate elevation of temperature and of the white blood count. Jaundice occurs occasionally. While a number of infarcts occur postoperatively, the majority are seen in "medical" patients and are more likely to develop in persons with cardiac disease. In a study by the author 6 per cent occurred after surgery, 70 per cent had evidence of heart disease and 24 per cent were noncardiac patients. Repeated examinations,

of necessity made at the bedside, are necessary because of the great variation in the appearance of infarcts and the frequency with which the infarct shadows are marked by various complications. All authors agree that infarcts occur most frequently in a lower lobe, especially the right. When an upper lobe is involved, infarcts will almost always be found in a lower lobe also. They vary in size from one cc. to an entire lobe. Once developed it will vary but little in size, but complications such as pneumonia, abscess and pleural effusion may cause an apparent increase. They are frequently multiple. There is no characteristic shape, but by the nature of the process, it must be so situated that it borders on at least one pleural surface. Therefore, the shape is modified by the contour of the portion of the lobe involved. It is possible for an infarct to have a conical shape and to present a roughly triangular appearance in the X-ray film; but, if so, it will be triangular in only one projection. Variations in shape will also be encountered as the result of a superimposed infarct shadow. Border of an infarct shadow is usually sharply demarcated and the shadow is almost always homogeneous after the first few hours and is of moderate density in relation to its diameters. The presence of complications may obscure the X-ray appearance, sometimes quite early. Roentgen examination should, therefore, be made as soon as possible after the onset of symptoms. Among the complications are bronchopneumonia, which may begin within a few days; pleural effusion, which is a distressingly frequent complication; secondary lung abscess within the infarct which is a not uncommon sequel. Pulmonary pleural fistula may also develop with resultant empyema. Many small infarcts heal. Healing occurs by replacement of the necrotic tissue by fibrous tissue resulting in a stellate or linear scar. Infarct shadows must be differentiated from pneumonias of various types, neoplasm, passive hyperemia, pleural effusion, cysts and atelectasis.—*Roentgen Diagnosis of*

Pulmonary Infarcts, G. R. Krause, *Radiology*, August, 1945, 45: 107.—(G. F. Mitchell)

Pulmonary Thrombosis.—Pulmonary thrombosis is rare in children. There have been only 14 cases reported in the literature since 1897. The literature is reviewed in this article and a case history given of a 7 year old boy who had recurrent "colds" with chills, fever and anorexia over an eight-month period. There had been occasional abdominal pain and hemoptysis. Two weeks before the onset of the above symptoms the boy had been involved in an automobile accident in which he had been knocked down, having been struck on the chest. At the time of the accident there had been no external evidence of injury. On admission to the hospital physical examination revealed that he was acutely ill, pale, temperature 102° F., pulse 120, respirations 48. Moderate cyanosis was present. The heart was enlarged to both the right and the left with a thrill present over the left third interspace. A loud harsh systolic murmur was heard over the precordium, loudest over the aortic and pulmonic areas. There was dullness over the entire right chest both anteriorly and posteriorly with bronchial breathing and increased breath and voice sounds present over the areas of dullness. The liver edge was tender and palpable four fingers below the costal margin. The spleen was palpable and enlarged. Clubbing and ankle edema were present. The tuberculin test was negative. Hemoglobin was 40 per cent, red blood cells 2,210,000, white blood cells 17,250 with 86 per cent polymorphonuclears. Admission X-ray film revealed extensive infiltrations in the inner zone of the right lung with less extensive infiltrations spreading out from the hilum of the left lung. The diagnosis was extensive pneumonitis, tuberculosis to be ruled out. There was no change on sulfadiazine therapy. The boy was discharged one month after admission unimproved. He died twenty-five days after discharge following two generalized convulsions. Autopsy revealed a congenital

anomaly of the heart consisting of inter-ventricular septal defect, thrombosis of the pulmonary artery with massive pulmonary infarction, abscesses of the lower right lobe, pulmonary edema, acute fibrinous pleurisy on the right, hypertrophy and chronic passive congestion of the spleen and liver and emaciation. There follows a discussion of incidence, pathogenesis, symptoms, signs, treatment and prognosis. It is pointed out that the differential diagnosis in children lies between congenital heart disease, heart failure with chronic passive congestion, pneumonia and tuberculosis.—*Thrombosis of Pulmonary Artery in Children*, Elinor B. Harvey & P. Hogg, *Am. J. Dis. Child.*, January, 1946, 71: 67.—(K. R. Boucot)

Traumatic Wet Lung.—The authors report observations and treatment on severely injured cases seen within a few hours of injury. They observed that (1) in all wounds of the chest to a greater or lesser degree, depending upon the type and severity of the lesion, the lung tissue reacts to produce more than its normal amount of interstitial and intrapulmonary fluid; and that (2) in all wounds of the chest the bronchopulmonary tree not only has more fluid to rid itself of, but becomes less capable of doing so. The "wet lung" may be present in a severe degree from a relatively minor lesion. Clinically these cases are often apprehensive, dyspneic, with paroxysms of painful cough which while productive is not effective in emptying the bronchopulmonary segments. On physical examination there is restricted motion and diminished breath sounds, with many moist bronchial râles, wheezes, ronchi. Some cases resemble bronchial asthma. Râles are usually heard on both sides and this is a valuable clue as associated conditions, hemothorax, pneumothorax, etc. may mask signs on the involved side. X-ray findings may be absent even in the presence of marked auscultatory moisture. The primary cause of increased lung moisture is not known, but seems to be related to the production of chest wall pain. "Wet lung" may be the antecedent stage of

massive collapse, and those who treat wet lung according to principles outlined here do not see massive collapse. In treatment only two points are paramount: control the production of moisture and promote bronchial drainage. Morphine and adhesive strapping are unphysiological. Temporary nerve block, or paravertebral sympathetic block, repeated as often as necessary, is the first treatment to be thought of, and frequently is the only treatment necessary. Results are often dramatic. The cough becomes painless and effective. One in a very few minutes into one of comparative comfort and safety. Others may require tracheobronchial catheter aspiration or bronchoscopy. Aspiration is particularly indicated in cases complicated by a bronchopleural fistula. When lung moisture persists after nerve block and effective cough or aspiration, intravenous atropine (grains 1/150) is of great value. In other cases oxygen delivered under positive pressure is of benefit. The differential diagnosis in these cases includes bronchial asthma, pulmonary edema of cardiac origin, pulmonary edema in peripheral vascular failure and blast lung. As blast lung is a severe degree of pulmonary contusion the resulting pulmonary edema is probably traumatic in origin, and treatment along the lines outlined here will be most beneficial: nerve block, catheter suction, atropine, oxygen under positive pressure. An interesting series of selected cases is presented illustrating vividly the application of the principles outlined.—*Traumatic Wet Lung*, Major T. H. Buford & Major B. Burbank, *J. Thoracic Surg.*, December, 1945, 14: 415.—(W. M. G. Jones)

Pulmonary Rarefaction.—Cyst-like pulmonary cavities, which are not the result of destruction of pulmonary tissue by inflammation, may be congenital or acquired. Congenital cysts often escape detection until later in life. The lining membrane is composed of cylindrical, cuboidal or flattened epithelium unless it has been destroyed by secondary infection. Congenital cysts may

produce no symptoms but cough, dyspnea and cyanosis may occur particularly in infants with expanding cysts due to check-valve mechanism. On X-ray examination, these cysts may be confused with an encapsulated empyema or a tension pneumothorax. Effective therapy requires removal, either by lobectomy or pneumonectomy; if possible, operation should be deferred until the patient is two or more years of age. Cystic bronchiectasis is regarded by some as one form of congenital cystic disease. Cystic bronchiectasis may be secondary to chronic bronchial obstruction. Where suppuration is present, particularly in the presence of bronchial obstruction such as a foreign body, it is frequently impossible to determine whether the cystic disease is congenital or acquired. Nontuberculous cavities in children may be due to evacuation of lung abscesses or to partial bronchial obstruction resulting in pneumatocele. Usually, cavities produced by lung abscesses diminish in size as the inflammation subsides. Where they persist, owing to fibrosis or epithelialization, surgery may be required. Pneumatocèles usually appear when pulmonary infiltrations are resolving and their development is not accompanied by purulent sputum or other pulmonary symptoms. Pneumatocèles commonly disappear in a few weeks or months and do not require surgery. They can be differentiated from other types of pulmonary rarefaction by serial clinical and X-ray studies. Illustrative case reports are cited.—*Annular Arcus of Pulmonary Rarefaction in Children, Eileen Phillips & C. A. Stewart, New Orleans M. & S. J., December, 1945, 98: 247.*—(H. R. Nayer)

Emphysema.—The fundamental elements of respiration are the extensibility and the elasticity of the lung tissue. The elasticity causes a continuous tension on the internal surface of the thorax and so maintains the negative pressure in the pleural cavity. This facilitates the circulation of the venous blood. The vital capacity depends entirely on the degree of distention and retraction of the

pulmonary parenchyma. The emphysematous patient has lost part of the pulmonary elasticity with increase of the extensibility. This causes permanent hyperdistension especially, during expiration. This, in turn, results in an increase of the air in the lungs which becomes an obstacle for the entering of new air into the alveoli. From the physiopathological viewpoint, pulmonary emphysema can be explained as a change in the pulmonary structure characterized mainly by permanent relaxation, dilation, diminution and finally loss of elasticity of the lung. This results in an increase of the volume of the lungs with change from negative into positive intrapleural pressure. The respiratory functions are profoundly affected by these changes. There is increase of the residual air with diminution of vital capacity. The effective amount of complementary air is considerably diminished by direct decrease of the tidal air and by relative increase of the dead space. The loss of elasticity causes in advanced emphysema an increase in the venous pressure. The intrapulmonary circulation suffers by compression of the capillary bed surrounding the distended alveoli. The quantity of blood in the pulmonary capillaries is diminished. This explains the cardiac symptoms of the emphysematous patient. The cardiac function itself is affected by the elongation of the vessels in the vertical sense. The difference between the pressure in the ventricles and in the great vessels is less than in the normal individual. The contractibility of the heart muscle fiber is diminished which effects the diastole. By Starling's law the systolic volume is therefore reduced. This results in cardiac insufficiency which does not respond to the usual treatments. The persistently high intrapleural pressure produces also the characteristic deformity of the thoracic cage which is increased in all its diameters and may finally be fixed in permanent inspiration. As the diaphragm is maintained in its normal dome-shaped position by the difference of the intrapleural and intraperitoneal pressures, an increase of the intrapleural pressure to around zero causes

flattening and descent of the diaphragm into the abdominal cavity.—*Características fisiopatológicas del enfisema pulmonar*, J. A. Sciuto, *Rev. de tuberc. d. Uruguay*, April, 1945, 13: 197.—(W. Swienty)

Bullous Emphysema.—Eight cases of progressive bilateral bullous emphysema, observed during a period of three years, are presented, and 13 similar cases, reported in the literature as bullous emphysema, giant bullous emphysema, cystic disease of the lungs, multiple cysts of the lung, cystic degeneration of the lungs, vanishing lung, are reviewed. All patients were men. The symptoms of cough, increasing dyspnea, recurrent infections of the respiratory tract, asthma-like attacks, weakness, loss of weight usually began in the third and fourth decades. The roentgenological examination showed emphysematous bullae in the upper lobes, appearing first in the apices and slowly extending downward. The lower lobes were compressed, the diaphragms were depressed. Little is known of the cause, pathogenesis and treatment.—*Progressive Bilateral Bullous Emphysema*, A. H. Price & G. Teplick, *Arch. Int. Med.*, February, 1946, 77: 132.—(G. C. Leiner)

Cystic Disease.—The authors define cystic disease as any condition in which the lung parenchyma is replaced by sharply defined cavities containing fluid or air; dermoid cysts, ecchinococcus cysts and encapsulated interlobar collections are excluded. Cystic lung disease may be congenital, acquired or both. Congenital cystic disease falls into two main groups: (1) The large solitary cyst which may occupy one or more lobes often displacing the mediastinum. These are usually discovered in infancy or early childhood giving symptoms of cyanosis and dyspnea. These cysts are lined by a layer of columnar epithelium resting on a tunica propria and a layer of connective tissue. Bronchial communication is difficult to demonstrate grossly. On the X-ray film, the cystic space is usually well defined. (2) In this type, the lung paren-

chyma is replaced by areas of cystic degeneration ranging from multiple miliary cysts to large multilocular or unilocular cysts. These cavities communicate freely with bronchi and the walls show the usual architecture of a bronchus including smooth muscle and cartilage. On X-ray pictures, this form of cystic disease is characterized by a honey-combed appearance. The absence of accompanying parenchymal infiltration or distortion of the thoracic cage is helpful in ruling out an acquired bronchiectasis. Acquired cystic disease is associated with respiratory infection, chronic bronchitis, pulmonary fibrosis and emphysema, or bronchial asthma. Any pathological lesion causing incomplete bronchial obstruction can produce this condition. Pathologically, the acquired form of cystic disease is indicated by the presence of coal pigment in the contiguous alveolar walls and existence of blebs and bullae at the periphery of the lung. On the roentgenogram, acquired pneumatocele is seen as a poorly defined annular shadow devoid, for the most part, of lung markings. Differentiation from localized pneumothorax may be difficult but can usually be made by a diagnostic pneumothorax and intracavitary pressure determinations. Uncomplicated cystic disease of the lungs rarely gives rise to symptoms. However, upper respiratory infections are often followed by infection in the cystic areas. The severe constitutional symptoms and cerebral complications associated with acquired bronchiectasis and pulmonary suppuration are not seen in these cases. In later life, increasing dyspnea often becomes a problem. Hemorrhage is a frequent complication and occurred in 4 of 13 patients observed by the authors. Spontaneous pneumothorax occasionally complicates the picture and one patient in this series developed a spontaneous hemopneumothorax. Thirteen illustrative case records are summarized.—*Cystic Disease of the Lung*, E. Klosk, A. Bernstein & A. E. Parsonnet, *Ann. Int. Med.*, February, 1946, 24: 217.—(H. R. Nayer)

Silicosis.—Every year 8 to 9 per cent of all

miners in Bolivia are incapacitated by occupational diseases, especially silicosis. As mine work represents the only base for the economy of the country, this is of highest importance. Four different types of dust have to be considered in their effect on the lung tissue: (1) inert, (2) irritating, (3) sclerosing and silicotic and (4) carcinogenic. The two first are without great pathological importance. Silicosis is the most important form of pneumoconiosis and has been made the object of this monograph. It is caused by inhalation of dust containing free silica and leads to progressive pulmonary fibrosis mainly of the nodular type. Some form of dust may be combined with silica. The danger then depends upon their percentage of silica. Many factors contribute to the development of the disease. Only dust particles smaller than 5 micra cause silicosis. The dimensions probably have to be between one and 3 micra. There is a low threshold of five million particles per cubic foot. Even permanent life-long exposure to this will not cause any harm. The high threshold is about one hundred million particles per cubic foot. This will always cause silicosis after a various length of time which depends largely upon the percentage of pure silica in the dust. Under equal conditions, certain individuals develop the disease rapidly, others only after long exposure. Here individual predisposition and the state of the protective mechanisms, especially the epithelium of the nasal cavities and of the bronchi play a rôle. Alcoholism, so frequent among miners, is a major factor in breaking down the defense mechanisms of the body. The time element of the exposure is very important. One to two years' work in dust with a high threshold of particles and a high concentration of silica may cause acute fatal silicosis. The dust particles are lodged in the alveoli where they immediately undergo phagocytosis and form the so-called dust cells. The silica causes the death of the phagocyte. Destructive fibrosis sets in which results in progressive obstruction of the lymphatics. True silicotic nodules are so formed. They have a diameter of one to 2 mm. and are disseminated mainly in the

medial portions of the lungs. If silicosis is not symmetrical there must be some other disease complicating silicosis. In the later stages emphysema, hypertrophy and dilatation of the right ventricle, thickening and symphysis of the pleura are constant findings. Most important symptoms are dyspnea, cyanosis, chest pain and cough. Hemoptysis is rare. There is a progressive reduction of the vital capacity of about 15 per cent in the moderately and about 25 per cent in the far advanced cases. X-ray examination is the most important means of confirming the diagnosis. The picture may vary from increase of the broncho-vascular and linear markings in the initial phase to the typical snowflake formation in the advanced cases. Silicosis in the initial or moderately advanced stage has to be differentiated from miliary tuberculosis, bronchial asthma, siderosis, passive pulmonary congestion, bilateral bronchiectasis, metastasis, mycotic infections and *polycythemia vera*; the advanced case from chronic fibrotic tuberculosis and tumor of the lungs or mediastinum. The complications of silicosis are pulmonary infection, cardiac failure, spontaneous pneumothorax and malignancy. The most common complication is tuberculosis. Statistics have shown that the incidence of tuberculosis among workers was 2.39 per thousand whereas in the presence of the dust it was 5.42 per thousand. Experimental studies have shown that dust inhalations diminish the relative immunity conveyed by the primary infection. The development of tuberculosis is directly related to the concentration of free silica in the dust. Tuberculosis is the cause of death of a third of all workers in the granite industry. From animal experiments the conclusion can be drawn that tuberculosis occurs as a new infection in the lung previously damaged by silica dust. The mixed lesions have a slow evolution but always terminate in an active tuberculosis. Two forms of tuberculosis, as complication of dust disease, can be differentiated: silico-tuberculosis and tuberculosis with silicosis. Silico-tuberculosis is characterized by modified silicotic lesions without

signs of active local tuberculosis. The typical lesion is a nodule of about 3 to 6 mm. in diameter with caseous centre and a periphery rich in cells but with only occasional giant cells. The mineral particles are in the periphery. By coalescence giant nodes develop. Clinically, in the beginning there are no symptoms of tuberculosis. X-ray films show the typical nodule and the tendency of the nodules to augment in volume and to become confluent. Finally there are massive dense shadows. Tuberculosis with silicosis is that state in which silicosis is complicated by active open tuberculosis. It includes the terminal stage of silico-tuberculosis. It occurs mostly in young individuals who have been exposed to dust for a relatively short time. There is no known treatment to check the progress of silicosis. Only by prophylaxis can decisive results be obtained. Sanitary measures consist in sprinkling of the mines, ventilation and aspiration of the dust. Every worker should wear a mask. Dust collectors should be installed. By projection of inoffensive floating particles into the air the diameter of the silica particles can be increased. Forced inhalation of inoffensive dust as metallic aluminum may retard or counteract the accumulation of silica in the lungs. From the medical standpoint, every worker should be X-rayed at regular intervals. The legislation for the protection of the miners in Bolivia is insufficient and very often not obeyed by the mine operators. It is suggested to change workers exposed to silica dust periodically into other healthier professions, especially in agriculture.

—*Neumoconiosis y silicosis, S. Medeiros Q., Ap. respir. y tuberc., Bolivia, 1944, 5: 42.*—
(W. Swienty)

Acute Silicosis.—This is a case report concerning an engineer, who became ill after four months of exposure to an atmosphere heavily loaded with mineral dust in a volcanic region in Honduras. The first phase of illness was characterized by a grippelike syndrome with fever, paroxysms of cough and diffuse erythema on the abdomen

and on the chest and scattered râles over the lung. A chest X-ray showed a diffuse, nodular, partly coalescing infiltration in both lungs. The sputum was negative for tubercle bacilli on repeated examinations. The clinical course was progressive and the patient eventually died from cardiac insufficiency. No postmortem examination was made. An assistant to this patient, who had accompanied him on his last trip, showed similar, but less extensive pulmonary lesions and a mild clinical syndrome. These 2 cases may be considered as acute silicosis. While pneumoconiosis is rare in Cuba, there have been described cases of "bagassosis" due to inhalation of cane grindings. The "bagasse" is a dusty material which constitutes the remnants of cane after the extraction of sugar. The clinical onset of bagassosis occurs usually after two to four months of exposure; it starts acutely with paroxysmal cough and dyspnea, sometimes blood-streaked expectoration, retrosternal pain and asthenia. The X-ray film of the chest shows enlargement of the root shadows and increased pulmonary markings. Complete resolution is possible in some cases, while in others there is a tendency to a chronic fibrosis. The "bagasse" contains 5 to 7 per cent of silica, but the disease in question cannot be considered a silicosis. It is probable that bagassosis is of allergic origin. Extract of bagasse gives a positive reaction in sensitized persons.—*Caso interesante de silicosis, aguda, bagazosis, M. A. Manas, Rev. mex. de tuberc., November-December, 1945, 7: 391.*—(L. Molnar)

Silicosis.—Bronchospasm is a factor in the dyspnea of the patient with silicosis, as seen from the fact that the patients are relieved by the administration of epinephrin. It has been shown that colloidal silica produces bronchospasm. Eosinophilia—which is usually considered to be part of a generalized allergic response—is found in over 50 per cent of patients with silicosis. Histamine produces bronchospasm in silicotics as it does in patients with bronchial asthma. It is believed

that silica has allergenic properties which are partially responsible for the dyspnea in silicosis.—*The Allergenic Effect of Silica and Its Relation to Dyspnea in Silicosis*, W. J. Habeeb, *Ohio State M. J.*, December, 1945, 41: 1101.—(G. C. Leiner)

Workmen's Compensation for Silicosis.—The new Czechoslovak law provides for a compensation for workers afflicted with pneumoconioses and consecutive tuberculous or carcinomatous lesions. Silicosis is an outstanding problem. Workers suffering from this disease receive medical care, including hospitalization, and a monetary compensation equal either to one-half year's full pay or 50 per cent of their former salary for life-time.—*The Disease of Foundrymen: Silicosis*, (Czech), E. Graubner, *Casop. lék. esk.*, July, 1946, 85: 995.—(O. Felsenfeld)

Dust Particle Size.—Determination of particle size of atmospheric dusts is important in evaluating health hazards in various industries. A sufficient number of particles (usually 150 to 200) is measured and the geometric mean size and standard deviation are then determined graphically. Various methods are used for measurement of dust particle size. The jet dust counter commonly used is selective for particles below 2.0 micra. Other methods involving evaporation of a dust sample solution on a glass slide are particularly unsatisfactory for fibrous dusts, such as asbestos, due to the tendency to agglomeration of the particles. The collection of dry dust by filter bag or directly from rafters or ledges is unsatisfactory owing to disintegration of more fragile particles. The author's method overcomes these objections especially for fibrous dusts. The method involves the settling of the suspended dust from a liquid medium (ethyl alcohol) onto the surface of a number 1 microscope slide glass cover, allowing the suspending liquid to evaporate slowly to dryness, and then mounting the cover glass, dust side down, onto a microscope slide. The dust deposit, thus being on the underside of the cover

glass, can be sharply focussed and measured by oil immersion. The Dunn dust counting cell is used as the settling chamber.—*The Preparation of Slides for Measurement of Dust Particle Size*, W. E. McCormick, *Pub. Health Rep.*, February 1, 1946, 61: 129.—(H. R. Nayer)

Hazards in Fire-brick Industry.—A study of the refractory brick industry in Kentucky was carried out with regard to the dust hazard. Two raw materials are employed: plastic and hard clays. These fire clays are basically hydrated aluminum silicates and they vary in chemical composition. The following average amounts of free silica were found: plastic clay, 17.7 per cent; flint clay, 7.1 per cent; semi-flint clay, 14 per cent; burnt brick, 10.3 per cent. Analyses of the dusts encountered in various operations ranged from 1 per cent free silica in some burnt brick dust to 95 per cent free silica in the mold or parting sand. The dry pan and screen mills are the most dangerous sources of sustained dust production; maximum concentrations of 2,742.2 and 1,176 million particles per cubic foot respectively were found at these points. The accepted safe limit is 5 million free silica particles per cubic foot. The median particle size of all atmospheric dust collected in the industry was three micra. Effective control measures are available for use in all operations of the industry.—*Siliceous Exposures in the Fire Brick Industry: I. Engineering Study*, W. W. Stalker, *J. Indust. Hyg. & Toxicol.*, December, 1945, 27: 275.—(H. R. Nayer)

Hazards in Fire-brick Industry.—An engineering study of the fire-brick industry revealed a sufficient volume of dust, containing enough free silica, to represent an industrial hazard. Chest X-ray films were made of 876 men in the industry. Ninety-seven (11 per cent) showed X-ray evidence of pneumoconiosis manifested by diffuse, finely granular fibrosis. These individuals had been employed in the fire-brick industry for periods ranging from nine to forty-seven

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years, the mean of their employment being twenty-five years. Two of the X-ray films showed nodular silicosis; these men had operated unenclosed dry pan mills for many years. Twenty-six X-ray films revealed evidence of tuberculosis; this represents a percentage exactly twice that found on mass surveys of the general population in this area. Eleven of these 26 cases were complicated by fine granular fibrosis.—*Silicosis Exposures in the Fire Brick Industry: II. Roentgenologic Study*, W. L. Riller & P. G. Bovard, *J. Indust. Hyg. & Toxicol.*, December, 1945, 27: 283.—(H. R. Nayer)

Beryllium Poisoning.—One hundred and seventy cases of beryllium poisoning were seen during a period of four years. Manifestations included dermatitis, chronic skin ulcer and inflammatory changes in the respiratory tract. The pathological findings and the clinical course of the disease suggest a chemical reaction as the cause. Ninety patients had chemical nasopharyngitis and/or chemical tracheobronchitis. The chief complaint of these patients was soreness of the nose and throat associated with mild epistaxis. Chemical tracheobronchitis was characterized by cough, râles in both lungs and normal serial roentgenograms. Vital capacity was reduced as much as 30 per cent in some cases. There was an occasional low grade fever. The illness lasted from seven to twenty-one days if exposure was discontinued. Chemical pneumonitis developed in 38 patients. Symptoms were cough with occasional blood-streaked sputum, substernal burning pain, dyspnea, cyanosis, abnormal taste, anorexia and increasing fatigue. The onset of the disease was insidious. The temperature was often normal. The sedimentation rate and the blood count were within normal limits. Roentgenological changes in the lung fields appeared two to three weeks after the onset of symptoms and physical signs. In order of appearance the changes were diffuse haziness of both lungs, development of soft irregular areas of infiltration with prominence of peribronchial markings, absorption

of soft infiltration and appearance of discrete large or small conglomerate nodules scattered throughout both lung-fields and clearing after one to four months. Five patients died of chemical pneumonitis. The pathological findings showed atypical pneumonitis. The lung tissue sections were characterized by large numbers of plasma cells, relative absence of polymorphonuclear infiltration, diffuse pulmonary edema and hemorrhagic extravasation. The most beneficial therapeutic measures were oxygen and rest. The incidence of beryllium poisoning dropped considerably after proper preventive measures were introduced in all three plants in which these 170 cases were observed.—*Beryllium Poisoning*, H. S. Van Ordstrand, R. Hughes, J. M. DeNardi & M. G. Carmody, *J. A. M. A.*, December 15, 1945, 129: 1084.—(H. Abeles)

Welding Hazards.—Welding in confined spaces without proper ventilation exposes the welder to serious danger from poisoning with oxides of nitrogen. When the acetylene torch is used for welding, the high temperature causes the formation of various oxides of nitrogen. The exact proportion of these gases depends on the prevailing temperatures. When inhaled a fairly constant proportion of nitrous oxide to 95 parts of dioxide. The latter polymerizes with further cooling to N_2O_4 . When these gases come in contact with water, as they invariably do in the respiratory tract, they form mixtures of nitrous and nitric acid. These acids cause severe purulent tracheitis, bronchitis, bronchiolitis and pulmonary edema. Several cases of death from pulmonary edema due to inhalation of oxides of nitrogen are on record, and the author adds another one. The welder was a young man in good health who had spent just twenty-five minutes welding inside a tank which was inadequately ventilated. When welding is done by means of electricity, the hazard is less, although it has been shown that oxides of nitrogen are also evolved, but to a lesser degree. The hazard in electric arc welding is further

reduced by the workers' wearing of a special protective screen.—*Nitrosegasevergiftung bei Schweissern*, F. Hatt, *Schweiz. med. Wchnschr.*, June 1, 1946, 76: 483.—(H. Marcus)

Asthma.—Severe asthma is best treated in a hospital, preferably in a private room. The new surrounding eliminates many nervous factors present in the patient's home. The pillows and the covers should be dust-proof. A pollen filter may be of advantage. The room should be free from drafts and fumes, the temperature should be even. The cleansing of the room is best done with a damp cloth. A mixture of 20 per cent oxygen and 80 per cent helium at a rate of flow from 6 to 9 liters per minute may give comfort in an acute asthmatic attack. The most useful drug is epinephrine. The usual dose is 0.5 cc. of a 1:1000 solution. This dose may have to be repeated at intervals of twenty minutes. A one per cent solution may be used as a spray. The critically ill patient may need epinephrine intravenously, one cc. of 1:1000 solution in one liter of isotonic solution of sodium chloride. If respiratory failure is imminent nikethamide or metrazole may be necessary. The intravenous administration of 0.25 g. of aminophylline in 250 cc. of a 20 per cent solution of dextrose may be of value. Aminophylline may also be given orally, 0.1 to 0.2 g. three times daily, or rectally 0.5 g. Ephedrine or ephedrine-like drugs are frequently used in combination with barbiturates and aminophylline. When bronchitis is a prominent factor an expectorant is of utmost value. Iodides are most helpful; if not tolerated ammonium chloride may be helpful. If nervous factors are prominent small doses of a sedative are indicated. If premenstrual tension causes an exacerbation of the asthma, estrogens should be used. Bronchoscopy has to be employed if broncho-stenosis is suspected.—*Treatment of a Seriously Ill Asthmatic Patient*, H. M. Carryer, L. E. Prickman, C. K. Maytum & G. A. Koelsche, *J. A. M. A.*, May 4, 1946, 131: 21.—(H. Abeles)

Asthma in Southwest Pacific.—Asthma has proved to be one of the important causes of chronic disability in the Armed Forces in the Southwest Pacific area. That asthma should recur or develop to a greater extent in the Armed Forces, either in the United States or overseas, than in the same age group among the civilian population, was not unexpected. The extremes of climate, increased exposure to dust and pollen, strenuous physical exertion and the emotional strain of military life would favor the recurrence or aggravation of mild asthma, and the development of new cases. The anticipated unfavorable effects of tropical conditions on asthma became apparent soon after our troops occupied certain islands in the Southwest and South Pacific areas. As more and more cases were being observed, the general aspect of the whole question assumed considerable importance and prompted the present study. Three hundred and fifty-two cases of asthma, representing 1.2 per cent of total admissions, were observed at a General Hospital in the Southwest Pacific Area. Of these, 209 were studied in detail, and an analysis of them is presented: 107 developed asthma prior to service; 102 after entering military service; 136 were inducted, 51 enlisted, 13 entered through the National Guard and 8 were officers; 109 were admitted from other hospitals, 98 from Base or unit dispensaries and 2 were not admitted but were studied in the out-patient department; 119 of 130 patients serving in the tropics experienced prompt aggravation or recurrence of symptoms, only 11 were not made worse; 66 patients developed their primary attack in the tropics. The rapidity with which aggravation or recurrence developed after arrival in the tropics was most striking; likewise, the primary attack appeared quickly but less so than the former. This sequence suggested an allergic mechanism. Development of asthma, either recurrence, aggravation or primary attack, was perennial; seasonal factors apparently exerted no influence. Pollen in the tropics and in Australian areas can be found throughout the year.

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A positive family or personal history of hay fever and/or asthma and of skin sensitivity to pollen and other inhalant antigens was found singly or in combination in the majority of patients. Conditions which aggravated or induced attacks in the susceptible individual were multiple; in addition to pollen and other environmental dusts, damp humid weather, diurnal temperature variations and physical and emotional strain were involved. After consideration of all the data, 115 or 55 per cent of the cases were considered as due to pollen and inhalant dusts; 29 or 14 per cent to infection and in 65 probable causes could not be defined. In these, however, environmental conditions probably played an important part. The disability rate per patient represented only by hospital days in this theater was rather high: the minimum was 5, the maximum 225, and the average 58.98; 172 patients, or 82 per cent of the entire series, were evacuated to the United States as unfit for duty in this area; 98 or 78 per cent of the 126 patients in whom asthma developed in the United States, either prior to or after entering service, were returned to the United States. Specific treatment, namely, desensitization to the dusts, was instituted. No conclusions concerning the efficacy of such therapy could be reached; in a small number of cases, such treatment appeared to be beneficial and enabled the patient to remain on duty. On the basis of this study, it is suggested that any soldier with a history of or manifesting mild asthma should not be sent to an overseas theater, unless limited or restricted service is understood. In any event such persons should not undertake tropical service. Even the presence of hay fever should be seriously considered as a disqualifying condition for general service overseas. Army Regulations—MR 1-9, dated 15 October 1942—state that bronchial asthma is disqualifying for military service. If this regulation were strictly adhered to, fewer cases of asthma would be overseas.—*Asthma—As Observed Overseas in a General Hospital in the Southwest Pacific Area*

—*With Special Reference to Relationship of Tropical Service to Onset and Recurrence*, W. L. Winklenwerder, Bull. Johns Hopkins Hosp., February, 1946, 78: 78.—(J. S. Woolley)

Surgery for Asthma.—The realization that bronchial asthma need not have an allergic nor a functional background has furthered interest in the operative treatment of this condition. The author has operated on the sympathetic nervous system of 43 asthma patients over a period of eight years. His results are in accord with those obtained by Leriche and Fontaine who found that 30 to 40 per cent of patients are cured permanently, another 40 per cent are considerably improved and 20 per cent are unimproved. The logical basis for these operations is the fact that the ganglia of the sympathetic plexus show severe degenerative changes in cases of bronchial asthma. Whether these changes are the cause or the result of the disease is as yet not known. In regard to the operative procedure it is stated that the exact point of attack on the sympathetic ganglia is not important. The author has found that his results are about the same whether he operates on one side, or on both, and whether he operates on the stellate ganglion or on the third cervical. In some cases the fibres of the vagus have been included in the operation, just below the origin of the recurrent branch. Theoretically, the best point of attack should be the ganglionated plexus at the lung roots, but this procedure is very difficult. It is remarkable that comparable results were obtained when the operation was confined to the ganglia of the lumbar sympathetic chain. These ganglia, on histological examination, showed identical severe degenerative changes. There are no complications from the operation other than a mild Horner's syndrome, which tends to disappear after some time, and a vasomotor rhinitis, which disappears after a few years. Serious complications are lacking, and the operation is deserving of trial in all asthmatics who cannot be benefited by medical treatment. The mode of action

of the excision of the sympathetic ganglia and plexus is not clear. It would appear that the entire vegetative system is intimately bound to humoral factors which act on the specific nerve tissue wherever it is located.—*Weitere Versuche zur operativen Behandlung des Asthma bronchiale*, K. Lange, Schweiz. med. Wchnschr., March 16, 1946, 76: 228.—(H. Marcus)

Premenstrual Asthma.—Certain cases of asthma are caused by ovarian insufficiency. If caused by hypofolliculinemia estrogens may be used with success. Sometimes the asthmatic attacks are directly related to the menstruation although the menstrual period may be completely normal and regular. This type of asthma may be caused by hyperfolliculinemia. It has been successfully treated with injections of corpus luteum. Clinically, there is swelling and pain of the breasts several days prior to the menstruation often followed by pelvic pain. During the menstruation there is a crisis of asthma, sometimes urticaria, fever, vicarious menstruation, nervousness, irritability and migraine. The authors have treated 6 cases of premenstrual asthma due to hyperfolliculinemia with testosterone. The relief with small doses of testosterone (5 mg. to not more than 50 mg.) was immediate in 4 cases. In 2 cases the treatment failed. This failure is attributed to recurrent infections which were found to be a sinusitis in one and an appendicitis in the other case.—*Asmas premenstruales*, J. M. Rodriguez Folgueras & I. P. Toulet, An. Cated. de pat. y clin. tuberc., December, 1944, 6: 327.—(W. Swienty)

Asthma.—Nine patients with intrinsic bronchial asthma were treated with penicillin. Penicillin was administered by intramuscular injections and, at a later date, intratracheally. Although there was slight clinical improvement it was felt that penicillin offered no advantage over the usual types of treatment.—*The Clinical Use of Penicillin in the Treatment of Intrinsic Bronchial Asthma*, S. F. Hampton, M. B. Wine, W. Allen, G. S.

Thompson & M. P. Starr, J. A. M. A., April 28, 1945, 127: 1108.—(H. Abeles)

Alveolar Cell Tumor.—The nature of cells lining the pulmonary alveoli, if any, and that of septal cells is still under debate and with this, the question whether carcinomata may arise from these cells. One case is presented of a very early tumor which presented the characteristics of an "alveolar cell tumor." But it was possible to show that this tumor originated in a bronchiole. Another case is presented of a primary adenocarcinoma of the gallbladder with metastases in the lung. The latter had all the gross and histological characteristics of "alveolar cell tumor." A study of 125 cases of pulmonary metastases showed that, if the primary tumor was a pure adenocarcinoma, the pulmonary metastases had the distribution of "alveolar cell tumors." It is believed that all so-called alveolar cell tumors are either metastases of recognized or non-recognized primaries in some other organ or true bronchial carcinomata arising from the basal cells of bronchi or bronchioli.—*"Alveolar Cell Tumor" of the Lung*, P. A. Herbut, Arch. Path., February, 1946, 41: 175.—(M. Pinner)

Primary Lung Tumors.—Over a period of fifteen years a histologically proved diagnosis of primary cancer of the lung was made in 157 patients. The incidence was highest between the ages of 40 and 50 years. It occurred four times as often in men as in women. The most common symptoms were cough, pain, sputum, hemoptysis and wheezing. A roentgenographic diagnosis of primary cancer of the lung was made in 152 cases, a positive diagnosis by bronchoscopy was obtained in 89.3 per cent of the cases in which the procedure was carried out (122 cases). Pleural effusion occurred in 26 patients. Carcinoma cells were demonstrated in 5 effusions. Biopsy of lymph nodes permitted the diagnosis in 26 patients. Pulmonary resection was carried out in 49 patients (31.2 per cent). Eight patients

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died in the hospital. The histological diagnosis was epidermoid carcinoma in 84 patients, adenocarcinoma in 20 patients, oat cell carcinoma in 7 patients. In 18 patients the tumor was undifferentiated. In 28 patients the tumor could not be classified. Seven cases of nonmalignant lung tumors were seen during the same period. All occurred in women.—*Primary Lung Tumors, R. Adams, J. A. M. A., March 2, 1946, 130: 547.*—(H. Abeles)

to be transmissible to men. It is still not clear if it is of neoplastic or infectious origin. The hyperplastic cells are non-ciliated and invade only the mucous membrane of the bronchioli and the alveoli. Differential diagnosis has to consider bronchial adenocarcinoma, histiocytoma and miliary tuberculosis.—*Consideraciones sobre un caso de adenomatosis pulmonar, R. C. Acevedo, L. S. Giuntini & O. C. Croxatto, An. Cated. de pat. y clin. tuberc., December, 1944, 6: 845.*—(W. Swicthy)

Malignant Lymphoma.—The histories of 3 patients with malignant intrathoracic lymphatic tumors are described. Attention is called to X-ray pictures resembling disseminated tuberculous infiltrations and exudative phenomena which may cause differential diagnostic difficulties. X-ray therapy is recommended; 2000 to 4500 r. total dose, according to the extent of the tumor.—*Difficulties in the Roentgenological Diagnosis of Lung Lymphomata, (Czech), M. Vitez, Casop. lek. česk., June, 1946, 85: 857.*—(O. Felsenfeld)

Pulmonary Adenomatosis.—The case of a 59-year-old man who was admitted with a picture of miliary tuberculosis and pleural effusion is presented. In the sputum, neoplastic cells were found. The patient died soon after admission and his condition did not allow a bronchoscopy or bronchography to be done. The autopsy showed that the left lung was invaded by a grayish-white tissue and was atelectatic. The right lung contained small seed-like nodules of elastic consistency throughout. The bronchi were normal. The microscopic examination showed that non-ciliated cylindric cells had invaded the alveolar wall but no mitosis or any atypical cells could be observed. The elastic tissue was somewhat increased but otherwise normal. The diagnosis during life had been blastoma but it was changed after the autopsy findings, to pulmonary adenomatosis. This disease common in South Africa amongst sheep and called "jaagziekte" or epizootic adenomatosis has been known

Cancer of Bronchus.—The literature contains conflicting reports regarding the value of radiotherapy in cancer of the bronchus. In the past, a large number of bad results were due partly to indiscriminate selection of cases. A radical course of treatment is given when there is hope of completely eradicating the disease. The patient must be in at least fair condition. The area involved must be limited in extent and there must be no lymph node or distal metastases. Severe sepsis must be absent; it is sometimes possible to undertake irradiation after diminution of the septic process by bronchoscopic aspiration and the administration of penicillin. The presence of pleural effusion prevents successful irradiation. Before a second course is given, it is necessary to be sure that the full effect of the first course has been achieved. Otherwise, severe post-irradiation changes in the lungs may ensue. Before irradiation of a case is undertaken, a complete investigation is made; this includes bronchoscopy, bronchography, tomography and sometimes thoracotomy. Of particular importance is the result of the histological examination. Radium and radon are not employed. The radical course of therapy is personally supervised daily by the radiotherapist and lasts six to seven weeks. Improvement in the patient's condition should appear in two to three weeks. During the four years 1940 to 1943, 179 cases of inoperable cancer of the lung were seen at University College Hospital. Eighty-four were considered too ill to receive radiation therapy. Of the

remainder 47 were considered suitable for a radical course of treatment, while 46 received only palliative treatment. The average duration of life in untreated cases was ten weeks. In those receiving palliative X-ray treatment, it was five months; generally there was some alleviation of symptoms. Of the 47 patients who received radical therapy, 12 were alive when the article was written, the average duration of life being 26.5 months. The 35 patients who died survived an average period of 11.4 months; all but 5 were able to return to work after the end of treatment.—*Radiotherapy in Inoperable Cases of Cancer of the Bronchus*, G. Hilton, *Brit. J. Tuberc.*, April-July, 1945, 39: 51.—(A. G. Cohen)

Biopsy in Lung Cancer.—A biopsy of the bronchial mucosa, even if apparently normal under bronchoscopic examination, may establish sometimes a positive diagnosis of epithelioma. Two cases are presented in which, clinically, a diagnosis of pulmonary carcinoma had been established. Although the mucous membrane of the involving bronchus appeared completely normal, a biopsy was done. It was found that the invasion had already reached the main bronchus and a previously contemplated pneumonectomy had to be abandoned. Systematic biopsy of the bronchial mucosa before operation is advocated in similar cases especially in that region where division of the root is contemplated.—*La biopsia de mucosa bronquial aparentemente sana en casos clinicamente sospechosos de cancer de pulmon*, A. Bence, J. Peroncini & J. C. Rey, *An. Cated. de pat. y clin. tuberc.*, December, 1944, 6: 334.—(W. Swienty)

Adenoma of Bronchus.—A study was made of 38 consecutive cases. The condition is more common in women. The average age of the patients was 37 years. The average duration of symptoms prior to diagnosis was twenty-six months. Hemoptysis was present in 54 per cent of cases but was the initial symptom in only 22 per cent; the character of the hemoptysis was no different from that

caused by any other type of bronchial lesion. Cough was present in 85 per cent. At first it was nonproductive. Later, with the development of infection secondary to atelectasis, the cough became productive of purulent sputum. Recurrent attacks of pneumonia in the same lobe were noted. Wheezing was noted in 23 per cent of cases. There was evidence of pulmonary suppuration in 23 per cent. Physical signs varied greatly. The tumor mass can at times be outlined by tomographic or by bronchographic studies. Atelectasis of the lung is indirect evidence of the presence of a tumor. The gross appearance of the neoplasm is so typical that the bronchoscopist can often make a correct diagnosis. The lesion appears as a pedunculated mass, the end of which is freely movable. It appears pink, red or purple and has a smooth surface which bleeds easily on contact. The diagnosis must, however, be confirmed by microscopic examination. There is a tendency for the adenoma to infiltrate the bronchial wall. It generally arises in a large bronchus, more frequently on the right. Various degrees of bronchiectasis with accompanying pneumonitis are found. Histologically, differentiation from carcinoma is not always easy. Mitotic figures are generally absent, as are evidences of degeneration of the tumor cells. The characteristic cell is small, round and regular; the nucleus is not markedly hyperchromatic. The cells do not vary in size. There are no metastases. The tumors are very vascular. If left untreated, the disease eventually kills the patient. In 14 cases where treatment was surgical, there was one death. In 22 cases treated by other means, there were 2 deaths. There is division of opinion as to whether endoscopic removal or extirpation by lobectomy or pneumonectomy is the preferable treatment. It is the authors' practice to employ the conservative form of therapy in those cases in which the adenoma is attached to the bronchial wall by a comparatively narrow pedicle, is easily movable and is situated in a readily accessible bronchus. It is also indicated when the tumor is close

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to the crura, or when the general condition of the patient precludes radical surgical treatment. Extirpation by lobectomy or pneumonectomy is indicated when the adenoma is located in a poorly accessible bronchus or where there is a marked tendency to recurrence. Roentgen therapy usually does not influence the size of the adenoma but at times seems to inhibit its development.—*Adenoma of the Bronchus*, H. J. Moersch, W. S. Tinney & J. R. McDonald, *Surg., Gynec. & Obst.*, November, 1945, 81: 551.—(A. G. Cohen)

Pulmonary Hodgkin's Disease.—The lung and pleura are not infrequently involved in the specific process of Hodgkin's disease. In a recent series of 273 successive cases treated at the University Clinic in Zürich, Switzerland, 25.6 per cent had pleural and pulmonary involvement. The pulmonary lesions are of three main types: perihilar infiltrations, representing direct extensions of the disease process from the mediastinal lymph nodes; massive parenchymatous lesions, probably originating by a lymphogenous route; and generalized hematogenous disseminated lesions. Pleural effusions are extremely common, but they are often due to the obstruction of the lymph flow or terminal cardiac failure. Primary Hodgkin's disease of the pleura is occasionally seen. The radiological picture in these cases to not sufficiently diagnostic, although the enlargement of the mediastinal nodes is suggestive. The picture can be confusing when cavitation occurs. This may be due to secondary infection or it may be the result of radiation therapy. The treatment of Hodgkin's type is the same as of the disease elsewhere, namely radiation therapy. The results are comparable and the disease is fatal after a period varying from a few months to several years.—*Les manifestations pleuropulmonaires de la lymphogranulomatosé maligne*, H. Perrier, *Schweiz. med. Wchnschr.*, December 8, 1945, 75: 1082.—(H. Marcus)

Miliary Carcinosis.—Four cases of cancer of the gastrointestinal tract (two of the gallbladder and one each of the stomach and pancreas) with miliary carcinosis of the lungs are reported. The tumor cells may reach the right heart via the hepatic veins or through the thoracic duct and the left subclavian vein. In all 4 cases the X-ray films presented evenly and diffusely distributed lesions, indicating hematogenous spread. The lesions appeared as soft, mottled, poorly defined areas of varying size. Hilar node involvement indicates secondary lymphatic spread. In the differential diagnosis, miliary tuberculosis and silicosis have to be ruled out. In the first, the lesions are more discrete and homogeneous and more nearly equal in size; the clinical picture, too, aids in the differentiation. In silicosis, the greatest involvement is in the midlung fields, the nodules are dense, discrete, uniform in size and there are usually dense hilar shadows and evidence of peribronchial fibrosis. Physical signs are absent in miliary carcinosis.—*Miliary Carcinosis of the Lungs Secondary to Primary Cancer of the Gastrointestinal Tract*, G. J. Culver, *Am. J. Roentgenol.*, November, 1945, 54: 474.—(P. Lowy)

Nondisabling Bronchiectasis.—Among 156,000 candidates for flying training, all of whom had at least one previous examination, 41 cases of bronchiectasis were discovered. Since there are few reports in the literature concerning mildly symptomatic or "dry" bronchiectasis, the authors are reporting this group. All the patients were ambulatory and were discovered on routine examination and had been in active service from two months to as long as two years. None had been incapacitated to any degree, though several had had pneumonia since entering the service. None had been to sick call an excessive number of times. No attempt was made to link the bronchiectasis with previous childhood diseases. All of the men tended to minimize their symptoms and considered their cough and expectoration as of no significance. While most denied all symptoms, even when

awaiting medical discharge, they now have some cough and expectoration of sputum. Information received from 36 men revealed 8 with no symptoms (one was reinducted by his draft board and, according to his medical officer, is asymptomatic), 2 have had unilateral lobectomies, 12 have symptoms so slight they are hardly noticeable, 8 feel well enough to perform their regular tasks in a satisfactory manner, 5 have moderately severe symptoms and have lost weight and are unable to work regularly and only 3 are under a physician's care. None of the group with symptoms have consulted a thoracic surgeon. Most of the men agreed that outside work in a dry climate seemed to relieve them. Typical cases are reported in detail. Among the 156,000 men X-rayed, 638 were found to have nontuberculous infiltrations, and most had these findings in one or both lower lobes. These men were admitted to the hospital where it was found that the majority had no or few symptoms. Many of them were believed to have atypical pneumonia. Only about 8 patients had lobar consolidation and in these the findings cleared at the end of two to three weeks. In about 100 cases, infiltrations persisted and accentuated peribronchial markings, ring-like transparent shadows or some recent pleuritic reaction were noted. Later, when these findings were encountered it became almost a routine to obtain a bronchogram. In addition to the 41, 4 men showed some dilatation of one or two bronchial radicles. Evans and Galinsky describe similar cases and raise the question whether these persons will go on and show progressive bronchial dilatation or whether the process is arrested and will finally disappear. It was decided to allow the men who, on close questioning, were asymptomatic and well to continue an army career. Of this group, 8 men continued to deny any symptoms, while 12 have symptoms so slight as to be almost unnoticeable. Only 3 were later available for reexamination and these showed no change. It has been suggested by Campbell *et al.* that bronchiectasis may develop in cases of atypical pneumonia that are slow to clear and have some associated atelectasis.

With this in mind, it would be desirable to obtain previous X-ray films, but in only 4 cases could this be done. One man was shown to have a previous bronchiectasis and one developed bronchiectasis subsequent to his pneumonia. However, among over 1,000 cases of pneumonia diagnosed by X-ray, 18 cases had persistent findings from four to six weeks. Of those who were bronchogrammed, none were found to have any bronchial dilatation. A recent Army Medical Bulletin suggests that discovery of minimal bronchial dilatation without symptoms should not be cause for dismissal from military service. This experience recorded by the authors seems to confirm the soundness of this policy.—*Non-Disabling Bronchiectasis*, A. Fine & T. B. Steinhäusen, *Radiology*, March, 1946, 46: 237.—(G. F. Mitchell)

Treatment of Bronchiectasis.—Forty-one per cent of all patients with bronchiectasis die within five years after the beginning of the disease from complications, such as right-sided heart failure, pneumonia, brain abscess, etc. Eighty-five per cent die within twenty years. The weakness of the bronchial wall increases the disproportions between the negative intrathoracic pressure and the positive atmospheric pressure in the bronchus. This purely mechanical factor causes distention of the bronchial wall and atelectasis of the surrounding tissue. This may lead to obstruction of the bronchus with dilatation of its distal portion. Medical treatment cannot cure the disease definitely as it is impossible to reestablish the normal anatomical structure of the affected bronchi. But the treatment can delay the progress of the disease. It is directed towards the suppression of local infections. An infectious focus in the sinuses or tonsils has to be removed. The respiratory tract should be inspected and obstructions caused by polyps, adenoids or a deviated septum should be removed. Adequate postural drainage is essential. In bilateral bronchiectasis, it should be done twice daily for a half hour on each side. Acute infections of the lungs and bronchi are treated with bed-rest, continuous oxy-

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gen therapy, penicillin and sulfa drugs. A correct analysis of the germs in the sputum as to their resistance to penicillin and the sulfonamides should be made before treatment is started. The results with penicillin are not as good as in other types of infection but are still very satisfactory. Nebulization of penicillin does not seem to give better results, so the author uses only the parenteral way; 15,000 to 20,000 units are given intramuscularly every three hours until 500,000 to 1,200,000 units are given. In penicillin-resistant cases sulfapyridine, sulfathiazole or sulfadiazine are given with equally good success. Poor results are given with vaporization of pure or mentholated water help to ease expectoration. It is very difficult to evaluate the results of purely medical treatment. The surgical cases are always selected unilateral cases with a good prognosis. All other cases are treated medically. There is no difference in the medical treatment for congenital or acquired bronchiectasis.—*Tratamiento médico de la bronquiectasia, R. Valdivieso D., Rev. méd. de Chile, September, 1945, 73: 781.*—(W. Swienty)

Penicillin in Bronchiectasis.—Twelve patients with severe bronchiectasis were treated with penicillin by intramuscular injection, intratracheal injection, inhalation or a combination of these methods. It was found that the intramuscular injection is not of help in the treatment of chronic bronchiectasis. Intratracheal injection of penicillin appeared most helpful, with reduction in the amount and odor of sputum and disappearance of the penicillin sensitive organisms in a period of time varying from a few days to several weeks. Excellent blood and urine concentrations of penicillin are also obtained by this method. The most useful plan has been to treat patients with intratracheal injection of penicillin, 100,000 units, for ten to twenty days, and then follow by injection or inhalation two or three times a week. The results are, of course, not permanent, and treatment has to be continued for an indefinite period of time. In spite of this, the treatment might be considered for

patients who are not fit subjects for surgery, or the treatment is suggested as a preoperative measure in surgical cases to lessen the danger of postoperative spread and empyema.—*Penicillin in the Treatment of Bronchiectasis, I. D. Bobrowitz, J. S. Edlin, S. Bassin & J. S. Woolley, New England J. Med., January 31, 1946, 234: 141.*—(H. Marcus)

Penicillin in Bronchial Disease.—Cases of chronic bronchial disease were treated by inhalations of nebulized penicillin. A solution of 25,000 units of calcium penicillin per cc. was used. Patients received 2 to 3 treatments a day. Each treatment consumed 100,000 units, which required about thirty minutes with the oxygen running at 8 liters per minute. A course consisted of a total of 1,000,000 units. The treatment resulted in clearance of the sputum of streptococci and pneumococci, but there was an increase in coliform bacilli. Cases of bronchiectasis showed no real improvement as indicated by the sputum output. Chronic bronchitis of the suppurative type showed no improvement; the dry type showed great improvement, but not permanently. Cases of asthma of the allergic type were not helped, but those of the infectious type showed real, though temporary, improvement.—*Inhaled Penicillin in Bronchial Infections, N. Southwell, Lancet, August 17, 1946, 2: 225.*—(A. G. Cohen)

Penicillin in Bronchiectasis.—Since in most cases of bronchiectasis there is a secondary infection of the dilated bronchi and bronchioles with a mixed flora in the sputum, often including bacteria susceptible to penicillin, it was thought that this antibacterial agent might have a beneficial effect in the treatment of the disease. It was clear that cure could not be obtained, but that symptomatic relief and preparation for a lobectomy when feasible would obtain. A high concentration of penicillin in the cavities could not be obtained by systemic treatment. Also, because of the nature of the disease, proper concentration could not be obtained by means of atomizers

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containing penicillin. It was therefore decided to inject a solution into the trachea, using a technique similar to that employed in carrying out bronchography. Following twenty to forty minutes of postural drainage a 14-gauge needle is inserted into the trachea between the cricoid cartilage and the first ring of the trachea. The needle is left *in situ*, the patient placed in such a position that fluid introduced would run into the diseased area, and then 5 to 8 cc. rapidly injected and the needle immediately withdrawn. The patient is kept in position for fifteen minutes after the injection. It was found that with an injection of 50,000 units the sputum coughed up twelve hours after the injection contained between 10 to 100 units of penicillin per cc. and with larger doses, that is, 80,000 units, the sputum after twenty-four hours still contained 10 units per cc. Daily treatment was carried out eight to ten days. Three cases were thus treated. An early case of bronchiectasis was so improved that the patient declined lobectomy. In the second case the patient was enabled to get over the later months of pregnancy and delivery without any extra difficulty arising from the chest condition. In the third case a patient who was clearly going downhill was rendered fit enough for lobectomy to be considered. The authors conclude that there would appear to be two uses for this form of therapy: (1) to improve the general condition of the patient before lobectomy; (2) to sterilize the bronchial cavities at regular intervals, especially during the winter.—*Infectious Bronchiectasis Treated with Intratracheal Penicillin*, H. B. May & M. A. Floyer, *Brit. M. J.*, June 30, 1945, 1: 907.—(D. H. Cohen)

X-ray Diagnosis of Bronchiectasis.—Bronchiectasis may be congenital or acquired. The congenital form is due to an abnormal embryological development of a bronchus and is often accompanied by other malformations, such as cystic lung, emphysema or bronchoalveolar agenesis. Those individuals may not have any symptoms of their bronchiectasis. Acquired bronchiectases develop after chronic inflammations of the respiratory tract.

Two forms may be distinguished, the cylindric and the saccular. The X-ray findings depend upon the contents of the bronchiectasis. If there is air in a saccular bronchiectasis, fine linear markings, which surround a clear space, can be seen. But air in a cylindric bronchiectasis may not give any X-ray evidence. If the contents are mucopurulent, diffuse shadows are seen in saccular, and thick linear markings in cylindric bronchiectasis. The bronchogram is the procedure of choice to demonstrate the presence of bronchiectasis. The cylindric form shows after filling with iodized oil a segmented column sometimes rosary-like. No peristaltic contractions are seen as the bronchial wall has lost its contractility. The saccular form shows the typical widening of the bronchi in which often a fluid level is present. Tomograms are necessary for exact localization.—*Diagnostico radiologico de las bronquiectasias*, F. Daza, *Rev. méd. de Chile*, September, 1945, 73: 774.—(W. Swienty)

Bronchiectasis and Dextrocardia.—Including the 2 cases reported by the authors, the literature contains reports of 50 cases of bronchiectasis and dextrocardia in the same patient. Studies of several series of cases of dextrocardia have shown an incidence of bronchiectasis of 16 to 23 per cent. This has indicated to a number of authors that the relationship is not purely coincidental but rather that the bronchiectasis is the result of a congenital defect.—*Dextrocardia and Bronchiectasis*, A. H. Russakoff & H. W. Katz, *New England J. Med.*, August 23, 1946, 235: 253.—(A. G. Cohen)

Lipiodol Reaction.—The chest roentgenogram of a 41-year-old man was suggestive of right basal bronchiectasis. There was no history of any allergic manifestations. The patient was prepared for a bronchogram with seconal and 3.5 to 4 cc. of a 10 per cent solution of cocaine. Ten cc. of lipiodol were injected into the base of each lung. Shortly afterwards he had a severe generalized convulsion. An intravenous injection of 0.5 g. of sodium amytal was given immediately but the patient

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became cyanotic and died a few minutes later. The pathological diagnosis was (1) obstruction, tracheobronchial, bilateral complete, due to inspissated mucus, causing massive pulmonary collapse and death from asphyxia; (2) bronchiectasis and bronchiolitis, mild to moderately severe, involving both lower lobes; (3) fibrosis, pulmonary, bilateral patchy disseminated, moderately severe. The possibility of cocaine poisoning was ruled out by the time interval and the pathological findings. It is felt that the patient was allergic to some constituent of lipiodol, probably the iodine. The immediate contact between allergen and shock organ produced a rapid and severe asthma-like reaction causing bronchial obstruction.—*Reaction following Bronchography with Iodized Oil*, G. S. Mahon, J. A. M. A., January 26, 1946, 130: 194.—(H. Abeles)

Bronchoscopy in Bronchiectasis.—Bronchiectases are found generally in the tertiary and minor bronchi and so are inaccessible to direct bronchoscopic examination. But bronchoscopy is the only way to differentiate bronchiectasis from pseudo-bronchiectasis. Sometimes several bronchoscopies are necessary. Pseudo-bronchiectasis develops subsequently to pneumonia or other respiratory infections. The bronchial dilatation is transitory but visible in the bronchoscope. No patient should be submitted to lobectomy without previous bronchoscopy. In bronchiectasis, thick, greenish, malodorous pus is found in the bronchus. The mucous membrane appears congested, edematous and bleeds easily. There may be considerable obstruction of the lumen by edema. Sometimes pus is adherent to the bronchial wall and forms a real tamponade with stenosis. Treatment consists of aspiration of the pus and reduction of the edema by instillations of ephedrine or adrenalin. The goal is to reestablish, as far as possible, the bronchial drainage. Installations of sulfathiazole, thioseptil and penicillin solutions directly into the affected area or by nebulizer give excellent results in the majority of the cases. If lobectomy becomes necessary the bronchoscope should be left in the affected

bronchus during the operation. Continuous aspiration prevents a spilling of the purulent secretion into the trachea and bronchial tree.—*La broncoscopia en la bronquiectasia*, A. Grez, *Rev. méd. de Chile*, September, 1945, 73: 778.—(W. Swienty)

Bronchiectasis.—Originally, in selecting cases of bronchiectasis in children for resection, the lobe was regarded as the smallest suitable unit. It was discovered that considerable amounts of healthy lung tissue were thus being sacrificed. This was an important consideration when several lobes were involved. In the past two years, cases have been selected on the bases of segmental involvement. The results of this policy as applied to 10 cases are reviewed. One of the lingula resection are not included. Cases of children underwent 3 segmental resections. There were no deaths and the morbidity was no greater than after lobectomy. The patients' ages ranged from 7 to 12 years and all had bilateral bronchiectasis. Meticulous pre- and postoperative care was carried out. A free pleura was found to be an advantage in permitting thorough palpation of the lung. Thus, involved segments were located which bronchography had failed to disclose. Before operation the bronchi were cleared by suction through the bronchoscope. The procedure was repeated at the end of the operation and sometimes during the course of it. Other technical features of the operation are described.—*Segmental Resection of Lung for Bronchiectasis*, R. Pilcher, *Lancet*, June 8, 1946, 1: 843.—(A. G. Cohen)

Surgery for Bronchiectasis.—Surgical treatment was carried out in 104 patients with bronchiectasis during the past two years. In 34 cases the disease was bilateral and in 6 of these cases bilateral surgical procedure was employed. In 8 cases pneumonectomy was done. A total of 110 operations were performed without any death. The poor long-range results of medical treatment justify surgical treatment on a large scale. There were 47 male patients and 57 female patients.

ABSTRACTS

The youngest patient was 2 years old, the oldest patient was 59. Unilateral disease was present in 70 cases, 40 of which were in the left lung and 30 in the right lung. In 62 per cent of the cases left lower lobe disease was associated with disease in the lingula. The association of bronchiectasis in the basal segment of the right lower lobe with localization in the middle lobe was observed in 42 per cent of the cases. Segmental resection was performed in 18 cases, in 10 of which double segmental resection, such as basal segment of the lower lobe and lingula, basal segment of the right lower lobe and middle lobe, or middle lobe and the anterior segment of the upper lobe. Segmental resection is particularly indicated in bilateral involvement. Postural drainage, penicillin both by injection and inhalation and sometimes bronchoscopic aspiration are useful measures to prepare the patient for the operation. The face down position of the patient seemed to be the most suitable during the operation. In the postoperative care the most important indication is to counteract surgical shock. The next important indication is re-expansion of the remaining lobes to fill the pleural cavity. Negative pressure drainage of the pleural cavity, expectorants, frequent changes in the position, the administration of analgesics are the measures that serve this purpose. In presence of atelectasis, bronchoscopic aspiration is indicated. Atelectasis was observed in 9 cases; it appeared on the second and third postoperative day. Empyema and bronchial fistula occurred in 4 cases, twelve days after surgery, empyema in 5 cases, twenty to thirty days after the operation and bronchial fistula two to fourteen days from the date of the operation. These complications occurred more often after segmental resection: empyema was three times more frequent after segmental resection than after lobectomy.—*Tratamiento quirurgico de las bronchiectasis*, L. Langer & H. Salvestrini, *Rev. méd. de Chil*, May, 1946, 74: 323.—(L. Molnar)

Bronchospirochetosis.—To the author it seems extremely doubtful that this condition

exists, nor has the existence of Castellani's spirochete been proved. Such a condition can only be diagnosed if chronic hemorrhagic bronchitis were present and spirochetes could be demonstrated in specimens from the trachea or bronchi. Another condition should be that the lungs are absolutely free of disease, since spirochetes can often be demonstrated in bronchiectasis and in broncholithiasis. No convincing case has ever been published and autopsy findings are not available. The disease has never convincingly been transferred to animals and it is significant that modern books on tropical medicine make no mention of this disease.—*Ist die Castellanishe Bronchialspirochätose ein wirkliches Krankheitsbild?*, E. Zimmerli, *Schweiz. med. Wchnschr.*, March 30, 1946, 76: 271.—(H. Marcus)

Foreign Bodies.—X-ray, laryngoscopy and bronchoscopy must be used for the diagnosis of such foreign bodies. Physical examination does not yield reliable results. The following foreign bodies were extracted: pin and bone from the larynx; dime, bean, nail, bone and the aluminum top of an aspirin bottle from the bronchi. A child is described in detail, who suddenly began to suffocate during a meal. X-ray examination and laryngoscopy were negative. Tracheotomy was performed. Bacteriological examination showed diphtheria bacilli. Early attempts at extraction of foreign bodies are recommended, before reactive processes set in.—*Foreign Bodies in the Respiratory Organs*, (Czech), E. Soukup, *Casop. lèk. èesk.*, July, 1946, 85: 970.—(O. Felsenfeld)

Foreign Bodies.—Five interesting cases of foreign bodies in the bronchus or esophagus of children are reported. Foreign bodies are less common in the bronchi than in the esophagus. On account of the more rigid structure and small diameter of the bronchus in children removal is always more difficult in these cases. Removal is also complicated by the fact that, unless the foreign body is impacted, it tends to move up and down the lumen of the bronchus with respiration and cough, thus causing irritation of the mucous membrane and producing a

varying amount of edema, which may ultimately occlude any view of the offending article. In the first case X-ray examination revealed an inhaled bead to be situated in the left main bronchus. Due to the smoothness of the bead it was impossible to grasp. A swab soaked in adrenaline was held against the mucous membrane around the bead for a few seconds; this resulted in shrinkage of tissues and after a few more attempts a firm grasp of the bead was obtained and removal ensued. The second case was one in which an open safety-pin was found, open end downwards, lodged in the oesophagus below the post-cricoid region. This was removed very easily—there being no need to close the pin before removal. The third case was that of a girl of 14 complaining of cough and pyrexia for two weeks prior to admission. There was clinical evidence of collapse of the right lung. Skiagrams of the chest revealed a very large paper-clip, with a round head and two prongs, lodged head downwards at the bifurcation of the right main bronchus. This was removed with extreme difficulty and with some damage to the tissues. The patient subsequently developed a complete collapse of the right lower lobe and a swinging temperature for a while, but with the help of sulphapyridine and breathing exercises she made a satisfactory recovery. In the fourth case a bent pin was removed from the region of the right main bronchus, with some difficulty in manipulation past the vocal cords. Other than a moderately severe laryngitis for a few days there were no ill effects. The last case was that of an 18 months old baby in whom an irregular piece of button was removed from the left main bronchus.—*Foreign Bodies in the Bronchi and Oesophagus in Children*, B. M. L. Abercromby, Brit. M. J., November 10, 1945, 2: 647.—(D. H. Cohen)

Pneumothorax following Bronchoscopy.—The common hazards of bronchoscopy are well known: direct injury to bronchus or nearby vessels, dangers attendant to anaesthesia, both local and general, subglottic edema and spontaneous pneumothorax. Author reports 6

cases of the latter, none of whom had foreign bodies, as he believes that insufficient attention has been paid to this complication. Indeed it should be kept in mind in all patients undergoing bronchoscopy, and especially in patients with diseased lungs in whom the stage is set for the occurrence of spontaneous pneumothorax. By far the commonest etiology is tuberculous, usually the rupture of a subpleural tuberculous focus, or of an emphysematous bleb. One case was proved to have spontaneous mediastinal emphysema. A consciousness of this complication in association with diagnostic bronchoscopy should prove life saving in some instances. More frequent use of the fluoroscope in suspected cases immediately after bronchoscopy is recommended.—*Spontaneous Pneumothoraces Occurring in Patients Undergoing Peroral Endoscopy*, O. A. Abbott & H. R. de Oliveria, J. Thoracic Surg., December, 1945, 14: 455.—(W. M. G. Jones)

Surgical Emphysema.—Two cases of massive surgical emphysema developing suddenly during or after intubation of the tracheobronchial tract are presented. The first case was one in which a diagnostic bronchoscopy was performed, uneventfully. A few moments after the bronchoscope had been removed the right eyelid became swollen. Very quickly the swelling spread to the face and neck. Deep cyanosis developed and respirations ceased. Laryngoscopy revealed the pharynx to be occluded by swollen spongy mucous membrane. Bronchoscope was introduced with difficulty and revealed the trachea to be occluded by grossly swollen mucous membrane. Further manipulation revealed occlusion of right main bronchus, but there was a very small passage in the much swollen left bronchus. Oxygen was directed into it through the bronchoscope and artificial respiration started. At this stage the abdomen was noted to be grossly distended and tympanitic. Two needles were introduced into the flanks and air at once hissed out. Spontaneous respiration soon came about, with improvement of the color. The bronchial swelling was seen to disappear within ten

minutes. Patient regained consciousness in four hours. An X-ray film of the chest and abdomen four days later revealed a right-sided pneumothorax and a considerable pneumoperitoneum. Another X-ray film ten days later showed neither pneumothorax nor pneumoperitoneum. Patient was discharged sixteen days after the incident symptomless, afebrile and free of physical signs, and has remained well since. Damage by the bronchoscope was the direct cause in this case, since no oxygen had been introduced. No real morphological explanation of this emphysema was possible. The second case was that of a boy 5 years of age admitted for bronchography under general anesthesia. Acute mediastinal emphysema and a bilateral shallow pneumothorax occurred as a result of a sudden delivery of oxygen into an intratracheal catheter, the accident being due to a faulty check-valve. Acute emphysema quickly developed, beginning with the eyelids and rapidly involving the face, neck and upper chest. Oxygen was given by mask and the child made an uneventful recovery. He was discharged five days after the incident, the radiograph taken on discharge showing that both lungs had completely reexpanded.—*Massive Surgical Emphysema, Pneumothorax, and Pneumoperitoneum*, B. Jones, *Brit. M. J.*, October 20, 1945, 2: 530.—(D. H. Cohen)

Blood Coagulation in Pleural Cavity.—This relatively simple matter has caused much controversy for over 100 years! Le Blanc and Trousseau in 1829 performed experiments on horses and concluded that (1) blood in the pleural cavity coagulates; (2) it does not cause irritation; and (3) it is readily absorbed. These conclusions are good to-day despite many statements to the contrary. Denny and Minot in 1915 repeated experiments of others and reached the conclusion that blood in the pleural cavity remains to a large extent fluid, not because of the presence of any "anti" substances, as some claimed, but because coagulation and defibrination produces a liquid that has all the gross appearances of whole blood, but in reality is only serum and cells. Elliot

and Henry, 1916, stated: "As blood flows from a wound into the pleural cavity, it clots rapidly. The clotting is not a massive coagulation such as one finds in a test tube of blood removed from blood vessels. The cardiac and respiratory movements agitate and whip the blood during coagulation, so that fibrin is thrown out and becomes deposited in layers of varying thickness on the parietal pleura and that part of the lung dipped into the effused blood. . . . This is a fluid which has at this stage no power to clot because it contains no fibrinogen . . . later an inflammatory pleural exudate is thrown out and added to the pool of liquid blood. If much fibrin ferment is still present . . . the fibrinogen of this exudate will also be coagulated. More frequently it escapes this change and then a sample of fluid taken from the pleural cavity exhibits a coagulation on standing which we term a secondary clot. This secondary clot has led . . . to the false conclusion that this is the primary clot. Absorption from the pleural cavity probably takes place as follows: substances in solution will be taken up by the blood stream, and particulate matter will be removed by the lymphatics either by way of phagocytosis or by direct ingress of the particulate matter to the lymphatic channel. Moreover if the aspirated fluid blood is studied on successive days after injury it is found that the percentage of hemoglobin rapidly falls while the percentage of fibrinogen rapidly rises. This suggests dilution by a reactive pleural exudate, which is most undesirable." The clinical application of all this is that "recovery from a hemothorax requires that the lung should reach the chest wall and obliterate any pleural cavity *at the earliest moment*. If fibrin develops before the pleural layers become apposed, the closure is mechanically delayed. Once fibrin has organized, it acts as a constricting barrier and encourages persistence of dead space and increases the risk of fibrothorax. This means full respiratory function is not recovered. This is the inevitable state of affairs in hemothoraces of appreciable size which are treated conservatively. The treatment of hemothorax should not therefore be conservative,

aimed only at preventing infection. It should be early evacuation of pleural blood and vigorous attempts to restore full lung expansion by breathing exercises. Even slight delay in evacuating the pleural cavity may incapacitate the patient for months instead of just a few weeks." Authors' experiments substantiate all these points. There is an excellent and complete bibliography on the subject.—*Experimental Hemothorax*, D. W. Melick & Maryloo Spooner, *J. Thoracic Surg.*, December, 1945, 14: 461.—(W. M. G. Jones)

Dry Pleurisy.—During 1943 and 1944, 20 cases were seen in the officers' ward of a general hospital in the Suez Canal area. Prodromal symptoms were rare. The onset usually was sudden. Pain was the first symptom in most cases and the chief symptom in all. It was pleuritic in character and was located in the lower chest, shoulders or upper abdomen. The severity varied greatly. The pain lasted three to twenty days, with an average of 10.7 days; the highest recorded temperature in each case varied from 99.2° to 104° F. Catarrhal symptoms were rare. A pleural friction rub was found in all cases. Cutaneous hyperesthesia was noted in 8 cases and abdominal tenderness in 6. Roentgenograms of the chest made in 18 cases were normal. Of 16 fluoroscopic examinations, 2 showed very slightly restricted motion of the diaphragm on the affected side. Leukocyte counts were essentially normal. There was complete recovery without complications in all cases. The literature was reviewed and comment made upon the great resemblance of cases in this series to previous reports of cases under the names "Bornholm disease," "epidemic pleurodynia" and "epidemic pleurisy."—*Acute Benign Dry Pleurisy*, J. G. Scadding, *Lancet*, May 25, 1946, 1: 763.—(A. G. Cohen)

Epidemic Pleurodynia.—Seventy-five cases of epidemic pleurodynia were seen on a small island in the Mobile River between June and November, 1944. The degree of infectivity was rather variable. Overcrowding seemed

to be a factor in the spread of the disease by contact. The outbreak of the disease was most prevalent among persons under 30 years of age. In 65 cases there was a history of an abrupt onset of the disease. More than half of the patients were practically afebrile. Pain and tenderness were present in the following regions in order of frequency: epigastric, subcostal, trapezius, costovertebral region, lower abdomen, right lower abdominal quadrant. Acute intraabdominal conditions have to be differentiated from pleurodynia. Frontal headache, dizziness and nausea were complained of by about half of the patients. The average duration of the disease was one to two weeks. All patients recovered completely.—*Clinical and Epidemiologic Aspects of Epidemic Pleurodynia*, S. J. Nichamin, J. A. M. A., October 27, 1945, 129: 600.—(H. Abeles)

Nontuberculous Empyema.—Five patients with empyema were treated by intrapleural instillations of penicillin without surgical drainage. The etiological agents were non-hemolytic staphylococcus aureus in 2 patients, pneumococcus type III, nonhemolytic streptococcus and a mixed infection of nonhemolytic streptococcus and hemolytic staphylococcus aureus in the other patients. Fifty thousand units of penicillin dissolved in 100 cc. of saline solution were administered at daily or two-day intervals following complete aspiration of the exudate. Underlying pulmonary disease or other complicating infections were treated by intramuscular injections of penicillin. Four patients with acute empyema recovered with little or no pleural thickening. One patient with chronic empyema with an acute exacerbation responded in the acute phase but eventually required further surgery.—*The Treatment of Empyema Thoracis with Penicillin*, M. J. Healy & H. L. Katz, J. A. M. A., June 23, 1945, 128: 568.—(H. Abeles)

Nontuberculous Empyema.—The indications for the use of penicillin in the treatment of empyema are as follows: (a) to cure small empyemata without loculation, lung sequestra or bronchial fistulae, (b) to make large empy-

emata smaller, (c) to tide over critically ill patients until they can be operated on safely. Empyema is cured when complete obliteration of the cavity is accomplished. It is rational to treat an empyema by aspiration of pus and instillation of penicillin as long as improvement is made; if this cannot be achieved surgical drainage should be done without further temporizing. Thirteen case histories are given as illustrations of the above statements.—*The Value of Penicillin in the Treatment of Empyema*, J. W. Hirshfeld, C. W. Buggs, W. E. Abbott & M. A. Pilling, J. A. M. A., June 23, 1945, 128: 577.—(H. Abeles)

Postpneumonic Empyema.—The basic objectives in the treatment of pleural empyema are sterilization of the exudate and obliteration of the pleural space by reexpansion of the lung. The best results are obtained when the development of dense pleural adhesions can be prevented. Hitherto, surgical drainage has been the mainstay in the treatment of postpneumonic empyema. The principle of allowing the exudate to become thickened lowered the mortality rate attendant in operating upon postpneumonic empyema; however, this also permitted the development of adhesions of the visceral pleura which, in some instances, prevented proper reexpansion of the lung. With the use of the sulfonamide drugs and penicillin to sterilize the pleural exudate, it became possible to utilize simple multiple aspirations as a definitive procedure. The authors detail their experiences with 14 cases of postpneumonic empyema treated with sulfonamides and repeated aspirations. In addition, 3 patients also received penicillin. Treatment was successful in all 14 without complication. Sulfonamides alone when given by mouth or intravenously in conjunction with thoracocentesis resulted in rapid sterilization of the exudate in 11 patients. Sulfonamides were not used locally. Penicillin was employed both parenterally and locally. Chest aspiration should be done early whether the empyema accompanies or follows pneumonia. The pleural space should be evacuated as completely as possible with each tap. Thoraco-

centesis should be repeated frequently at intervals of one or more days as the exudate forms and should be continued until no further fluid is found. Replacement of fluid with air was not done. The authors believe that this method should be applied routinely in postpneumonic empyema. The procedure of allowing the pleural exudate to thicken and performing a thoracostomy should be applied only when chest aspiration cannot be safely used because of the location of the exudate or where the infecting organism is resistant to sulfonamides and penicillin.—*Treatment of Postpneumonic Thoracic Empyema with Sulfonamides, Penicillin and Repeated Thoracocenteses*, A. I. Josey, J. W. Trenis & W. F. Kammer, *Ann. Int. Med.*, November, 1945, 23: 800.—(H. R. Nayer)

Penicillin in Acute Empyema.—In an attempt to establish the most effective treatment of empyema following pulmonary suppuration, the authors have compared a series of 24 cases treated with penicillin and 14 cases treated without. The best plan of treatment was found to be the aspiration of pus and instillation of penicillin into the pleural cavity at first, and drainage by intercostal catheter after the pus had thickened. The amount of penicillin to be instilled depends on the clinical phase of the patient's underlying disease. If the patient is still toxemic and the systemic condition requires treatment, 60,000 units of penicillin are given twice daily, or if aspiration is performed every other day, 240,000 units are given. If the effusion is frankly purulent and the patient's general condition is satisfactory, only 500 units are given. This can usually be done in pneumococcal infections, whereas staphylococcal infections require intensive and prolonged treatment. The sooner fluid is recognized, and the sooner local treatment is begun, the better the result. However, even if sterilization of the pus is obtained by early local treatment, intercostal drainage is usually still indicated because the pus thickens even if sterile so that it cannot be evacuated through a needle. After underwater drainage is established negative Gram

stains and cultures for three successive days indicate true sterilization. The tube is then withdrawn and a dressing placed over the wound which is left undisturbed for five to seven days. The presence of a bronchopleural fistula is no contraindication for treatment, except that possibly higher local doses of penicillin are necessary to compensate for the loss of drug in the sputum. Rib resection with or without administration of penicillin is not considered satisfactory treatment for the condition because of the high incidence of pyogenic infection from the outside. With penicillin treatment, the time from onset of disease to healing was cut down from fifteen weeks to seven weeks, and the time from institution of drainage to healing, from 11.6 weeks to 3.6 weeks.—*Acutely Infected Pleural Effusions*, L. Fatti, M. E. Morcy, H. Joules, J. H. Humphrey & J. Sakula, *Lancet*, March 2, 1946, 250.—(H. Marcus)

Putrid Empyema.—Two cases of putrid empyema due to ruptured lung abscesses were treated with combination of sulfadiazine and penicillin. Penicillin was administered intramuscularly and intrapleurally following repeated thoracocenteses. Treatment resulted in rapid improvement and cure. One case of postpneumonic empyema was treated with penicillin intramuscularly and intrapleurally following repeated thoracocenteses, with rapid improvement. One case of postpneumonic empyema, apparently caused by staphylococcus aureus and staphylococcus albus, was treated with penicillin locally, following aspirations of pus, with progressive improvement and cure. One case of empyema, apparently caused by staphylococcus aureus and proteus vulgaris, was treated with sulfadiazine orally, repeated thoracocenteses and azochloramid intrapleurally, with rapid cure. (Authors' Summary)—*The Medical Treatment of Acute Empyema: Report of Five Cases Cured with Chemotherapy and Thoracocenteses*, H. Rudensky, D. H. Sprong & C. C. Woods, *J. A. M. A.*, June 23, 1945, 128: 573.—(H. Abeles)

Putrid Empyema.—This disease is an entity separate from the usual postpneumonic empyema, both as to etiology and pathogenesis and as to prognosis and treatment. It is secondary to a pulmonary process of varying etiology. It is not uncommonly seen following putrid lung abscess, but the underlying pulmonary process may be a pneumonitis, bronchiectasis, tuberculosis or carcinoma with bronchial obstruction. The organisms involved are most commonly fusiform bacilli, anaerobic streptococci or microaerophilic streptococci, either alone or in combination. Patients with this disease are severely ill, and the fatality is high if treatment is not promptly instituted. Thoracocentesis is often followed by cellulitis of the chest wall and operation should follow this diagnostic procedure promptly to avoid this complication. The pus in putrid empyema remains thin for a long time and one should not wait with operation for the pus to thicken. In spite of the thin consistency of the pus, the mediastinum becomes fixed very early. A technique is described for operation should the mediastinum not be fixed. The best results are obtained with open resection, in which case the fatality was 14 per cent. Activated zinc peroxide has been found useful in dressing the wound. Two recent cases have been treated with penicillin and this drug appears to have great value in the treatment of anaerobic empyema. Although cure may not be obtained, the pus is sterilized and the condition of the patient is improved to the point where operation can be performed at an elected date.—*Putrid Empyema*, J. W. Strieder & J. P. Lynch, *New England J. Med.*, January 3, 1946, 234: 1.—(H. Marcus)

Hydatid Disease of Pleura.—Pleural echinococcosis is a rare disease. It may be primary or secondary. The primary form has been observed only in 2 undisputed cases. Secondary hydatid disease of the pleura is more frequent. It may occur after rupture of a cyst from any neighboring organ into the pleura. After rupture of a hydatid cyst of

the lung, only 10 per cent have subsequent pleural localization of the disease, whereas 80 per cent of a ruptured cyst into the abdomen have a localization in the peritoneum. This seems to prove that there are certain conditions in the pleura which make the insertion and growth of the parasites in the pleura less frequent. Secondary hydatid cyst of the pleura may be caused by surgical opening of the cyst, by a rupture of a cyst into the pleura which is the most frequent cause or by a spontaneous hydatid pneumothorax. Of this last condition, there are only 5 cases described in the literature to which the authors add a sixth one. This was a 15-year-old girl who was seen first with the diagnosis of a spontaneous pneumothorax. She had no cyanosis or dyspnea. X-ray examination showed a left hydropneumothorax with a hernia of the upper mediastinum and a considerable shift of the mediastinum into the right hemithorax. Overlying the fluid level and intimately connected with the diaphragm and the heart shadow was a round shadow of orange size, which contained an irregular density. There was an eosinophilia of 9 per cent. The Casoni and Ghedini reactions were negative. Thoracoscopy established the diagnosis: hydropneumothorax due to ruptured hydatid cyst of the lung with dissemination of multiple hydatid cysts into the pleura.—*Equinococcosis pleural multiple, consecutiva a un neumotorax hidatidico*, R. F. Vaccarezza, G. Pollitzer & F. A. Medici, *An. Cdled. de pat. y clin. tuberc.*, December, 1944, 6: 338.—(W. Swienty)

Echinococcus of Pleura.—There is no evidence of the existence of primary echinococcus disease of the pleura. The secondary implantation of the disease in the pleura is a rather rare occurrence, but its existence is definitely proved. True secondary echinococcus has to be distinguished from the pleural manifestations of bronchogenic and subdiaphragmatic localizations; localizations in the ribs and veterbrae may also involve the underlying pleura. The pleural form of the disease is caused by spontaneous or surgical inoculation into the pleural cavity. Seven cases were observed: the primary lesion was situated in one case in the pericardium, in 2 cases in the liver and in 4 cases in the lung. The inoculation occurred spontaneously in one case; in 4 cases surgical maneuvers produced the implantation and in one case trauma to the right hypochondrium caused the spread of the disease to the pleura. In 6 cases the cysts developed isolated, while in one case they formed a vesicular mass occupying the pleural cavity. The evolution is gradual and often silent. The disease is usually revealed by the break-through either to the chest wall or to the bronchial tree. The diagnosis is based on a preecedent history of hydatid disease, on X-ray findings, on serological tests and on blood counts. Early intervention in echinococcus disease and careful surgical technique constitute the best prophylaxis of the secondary pleural implantation of the disease. Once established, the pleural echinococcus is also treated surgically. Sometimes multiple surgical operations are necessary for the complete removal of all the cysts; the results are usually satisfactory.—*Equinococcosis pleural secundaria*, V. A. Ugon, A. Victorica & H. Suarez, *Hoja fisiol.*, September, 1945, 5: 245.—(L. Molnar)

Cyst of Diaphragm.—A primary cyst of the diaphragm of undetermined origin is reported in a 29-year-old man. He had occasional radiating pain, starting at the left costal margin, on deep inspiration or on bending and lifting. Chest roentgenogram showed a rounded protrusion near the left costophrenic angle, partly calcified (the accompanying X-ray reproduction is technically so poor as to be totally uninformative). The cyst was excised and patient made an uneventful recovery. The cyst wall consisted of an inner single layer of cuboidal epithelial cells and dense collagenous tissue. The cyst cavity contained old blood with cholesterol crystals. It is stated that 14 cancerous and 19 noncancerous primary

diaphragmatic tumors are on record since 1868.—*Primary Cystic Tumor of the Diaphragm*, O. B. Scott & D. R. Morton, *Arch. Path.*, June, 1946, 41: 645.—(M. Pinner)

Mediastinal Emphysema.—Air may reach the mediastinum by four routes: (a) along the fascial planes of the neck, (b) through a perforation of the trachea, bronchus or esophagus, (c) from the retroperitoneal space and (d) from the interstitial tissues of the lung. The most common cause of mediastinal emphysema is rupture of pulmonary alveoli with the production of interstitial emphysema of the lung. Circumstances that cause interstitial emphysema of the lung are: (1) trauma, injury to the chest with or without fracture of the ribs; operations, such as induction of pneumothorax; (2) increase of pulmonary pressure, straining with the glottis closed; partial or complete occlusion of the trachea or bronchi; (3) spontaneous rupture of alveoli, possibly due to an inherited defect of tissue quality. Air may escape from the mediastinum into the subcutaneous and deep tissues of the neck, through the diaphragm and into the pleural cavities. Air in the tissues of the neck does not necessarily indicate the presence of mediastinal emphysema since this may occur secondary to wounds of the chest communicating with the lung or to injuries to the buccal or nasal cavities. Experiments and clinical observations show that air from the mediastinum frequently enters the pleural cavity but that air from the pleural cavity never enters the mediastinum. The usual cause of tension pneumothorax following injury to the chest is not a valve-like mechanism but rupture of pulmonary alveoli with the formation of interstitial emphysema, then pneumothorax through rupture of the mediastinal pleura. The clinical manifestations of mediastinal emphysema are pain, subcutaneous and retroperitoneal emphysema, obliteration of cardiac dullness, peculiar sounds heard over the heart, evidence of mediastinal pressure, dyspnea, cyanosis, engorged veins, circulatory failure, pneumothorax and roentgenographic

evidence of air in the mediastinum. Pneumothorax is associated with spontaneous mediastinal emphysema in about one-third of the cases. Slight mediastinal emphysema may not cause any symptoms. Roentgenographic examination should be carried out in the anteroposterior and lateral views. No treatment is necessary if there is only a small amount of air in the mediastinum. When the pressure in the mediastinum rises it becomes imperative to furnish an exit for the trapped air.—*Mediastinal Emphysema*, L. Hamman, *J. A. M. A.*, May 5, 1945, 128: 1.—(H. Abeles)

Displacement of Mediastinum.—Mediastinal displacements are caused by pressure differences in the two sides of the chest. Such differences may be produced by increase in pressure on one side with displacement to the contralateral side, such as is seen in pleural effusions or tension pneumothorax. On the other hand, displacement may be caused by bronchial obstruction with displacement of the mediastinum to the homolateral side. This is most often seen in postoperative pulmonary collapse. When the mediastinum has been fixed by previous inflammatory disease, no displacement can be expected in spite of great pressure differences. Occasionally the greater portion of the mediastinum remains fixed and variations in pressure give rise to anterior, more rarely posterior, herniations. Herniations can be produced by pressure or by traction, just as mediastinal displacement in general. Recognition of mediastinal herniation caused by traction is of special practical significance. A case is cited in which pleural puncture was done on the left side prior to contemplated suction drainage of a large cavity in a retracted lung. This led to a traumatic pneumothorax on the right side due to a previously unrecognized herniation of the right lung well beyond the anterior axillary line on the left. The condition was demonstrated at autopsy.—*Die Verlagerung des Mediastinums in ihrer praktischen Bedeutung*,

A. Brunner, Schweiz. med. Wchnschr., Feb-
ruary 23, 1946, 76: 145.—(H. Marcus)

root anesthesia. In one case an osteo-
chondro-fibroma, in the other a dermoid cyst
was extirpated.—*Two Cases of Thoracic
Surgery, (Turkish), A. Aksel, Türk. tib
cem. mec., January, 1946, 12: 29.—(O.
Felsenfeld)*

Mediastinal Teratoma.—The clinical
course, roentgenological appearance and
pathological findings in 16 patients with
teratomata of the anterior mediastinum are
reported. In 10 patients the tumor was
benign and in 6 it was malignant; all the
latter patients died. The average survival
time after onset of symptoms was five-and-a-
half months. In the group of benign terato-
mata, 2 patients had no symptoms, 5 had
pain in the chest and later on cough and
dyspnea, 3 were short of breath. Seven
patients recovered following surgical removal,
2 died during the postoperative period and
one died from compression of mediastinal
structures. The 6 patients with malignant
teratomata had initial symptoms similar
to those with benign tumors, while later in
the course, symptoms were determined by
the extent of the primary tumor and the
location of metastases. The latter occurred
in liver, vertebra and lymph nodes. Fully
differentiated tissues and organoid deriva-
tives consisted in nerve tissue, skin and
teeth; but in the cancerous teratomata nerve
tissue was identified in only one case. The
benign specimens contained intestinal, bron-
chial and pancreatic tissue. In the malignant
tumors, epithelial cells were always arranged
as adenocarcinoma. The morphogenetic
theories are discussed and the conclusion is
reached that extragonadal teratomata are
"the result of a local dislocation of tissues
during embryogenesis." The tissue of origin
for teratomata of the anterior mediastinum
is probably dislocated tissue in the anlage of
the thymus.—*Teratoma of the Anterior Medi-
astinum in the Group of Military Age, H. G.
Schlumberger, Arch. Path., April, 1946, 41:
398.—(M. Pinner)*

Mediastinal Tumors Removed by Surgery.
—The histories of 2 female patients are
described in whom mediastinal tumors were
found. Surgery was performed in local and

Intrathoracic Sympathetic Nerve Tumors.—
Sympathetic nerve neoplasms are found in
many organs. In the thorax, they are
neither common nor rare. They are most
often asymptomatic and are frequently
discovered accidentally. The literature con-
tains reports of 63 cases. Of these, 43 are
listed as ganglioneuroma, 16 as sympathico-
blastoma (neuroblastoma), 2 as sympathico-
gonioma and 2 as pheochromocytoma. The
author reviews these cases as well as 7 of his
own. Numerous classifications of these neo-
plasms have been proposed, resulting in
conflicting terminology. The author prefers
Bielschowsky's classification which is based
upon embryological considerations. The
name of the tumor arising from the type of
cell is given parenthetically. The most
primitive and totally undifferentiated cells
are the sympathogonia (sympathogonioma).
These give rise to one of two chains: (1)
sympathoblasts (sympathoblastoma) which
become mature sympathetic ganglion cells
(ganglioneuroma), and (2) pheochromoblasts
(pheochromoblastoma) which become the
chromaffin cells (pheochromocytoma) of the
adrenal medulla and other organs. Often
more than one cell type is seen in a tumor.
It is believed that the terms neuroblastoma,
sympathoblastoma and sympathicoblastoma
have, in the past, been used interchangeably
to designate tumors composed of an immature
type of cell. Sympathogoniomas are very
malignant. They are very rare in the chest,
only 2 cases having been reported. The
tumors are very cellular, consisting of closely
packed cells of a lymphoid type. Rosettes
were seen in one-third to one-half of cases.
Metastases are frequent. Sympathoblasto-
mata are more mature and less malignant.
They are found in somewhat older persons.
They are rare in the chest. Sixteen cases

(16.6 per cent of total) have been reported. All these cases have contained more than one type of cell. Nerve fibrils are seen in large numbers; differential stains are often needed for their identification. Gangliomata are composed of mature cells rich in plasma. They are firm, encapsulated and may be lobulated. Microscopically, they consist of coarsely arranged fibrous tissue mixed with strands of medullated and non-medullated nerve fibers, the latter predominating. Multipolar ganglion cells are scattered throughout. Not infrequently these are multinucleated, indicating an element of immaturity. There are other tumors which are predominantly fibrous but contain varying numbers of ganglion cells and are called ganglion neurofibromata. While gangliomata are generally benign, cases where they were malignant have been reported. Chromaffin tumors are very rare in the thorax, only 2 cases having been reported. They consist of large polyhedral cells in a rich vascular stroma. The cells have an affinity for chrome stains. Dumbbell tumors are present both in the spinal canal and among ganglioneuromata. They are usually fibromata may be of sympathetic origin. Even those found along intercostal nerves may have their origin in sympathetic nerve elements.—*Intrathoracic Tumors of the Sympathetic Nervous System*, R. K. Hollingworth, *Surg., Gynec. & Obst.*, June, 1946, 82: 682.—(A. G. Cohen)

Anterior Mediastinal Abscess.—The anterior mediastinum is, for the most part, protected by fascial layers against direct infection from the nasopharynx or cervical regions. Direct infection of the anterior mediastinum from without can occur in perforating wounds. Tuberculosis, syphilis and actinomycosis have been common causes of anterior mediastinitis. In general, inflammation of contiguous structures such as the sternum, mediastinal lymph nodes, pleura and pericardium has been implicated in

anterior mediastinal suppuration. The constitutional signs and symptoms of suppuration are usually present. Localizing signs may be entirely lacking or are very confusing. Commonly, there is chest pain though not always retrosternal. As the abscess increases in size, there is more likely to be complaint of substernal oppression and the signs of pressure on the heart, great vessels and trachea begin to appear. Electrocardiograms taken at this late stage may show T wave and ST changes similar to those described in pericardial effusion or coronary disease. Roentgenograms, particularly lateral views, are valuable in diagnosis. Definite diagnosis is established by aspiration. While chemotherapy is a helpful adjunct, surgical drainage is the specific treatment. Two illustrative case reports are cited. In the second patient who came to autopsy, there was evidence of the spread of a suppurative process from a perforated appendix to the liver and thence to the diaphragm. Pleuritis ensued and the infection apparently spread to the anterior mediastinum.—*Two Cases of Anterior Mediastinal Abscess*, M. Aronovitch & A. M. Vineberg, *Canad. M. A. J.*, November, 1945, 53: 455.—(H. R. Nayer)

Esophageal Atresia and Tracheo-esophageal Fistula.—A case is reported of congenital atresia of the esophagus and associated tracheo-esophageal fistula. Operation was performed on the second day. The fistula was closed and the esophageal segments were then joined by an oblique anastomosis. The baby was discharged on the nineteenth postoperative day.—*Correction of Esophageal Atresia and Tracheo-Esophageal Fistula by Closure of Fistula and Oblique Anastomosis of Esophageal Segments*, R. E. Gross & H. W. Scott, Jr., *Surg., Gynec. & Obst.*, May, 1945, 82: 519.—(A. G. Cohen)

Pain in Chest.—During the past two decades physicians and lay public have become increasingly aware of the frequency and seriousness of coronary artery disease, and the erroneous assumption is often made

by the patient and physician that substernal or precordial pain, especially if it radiates to the left arm, is due to such disease. An attempt is made here to investigate points significant in differential diagnosis with especial emphasis on the qualities of the pain, often the only means of diagnosis. Disorders of the alimentary tract often produce pain in the chest. One-sixth of a series of several hundred patients complaining of this symptom had disease in the alimentary tract, and one-fifth of these was due to the esophagus or about 4 per cent of those with chronic or recurrent chest pain. The chief causes of distress were esophagospasms. The pain was substernal and did not radiate. X-ray examination was negative in all. The location, duration and quality of the pain closely resembled angina pectoris; however, the precipitating factors were entirely different and not in one was it induced by exertion. Often it was induced by eating, and lasted longer than the usual anginal pain. In others it was initiated by eating, recumbent position, highly seasoned food or alcoholic beverages. Some were demonstrated by radiological examination during an attack of pain or by esophagoscopy examination. Antispasmodics, especially those of the atropine group are the most beneficial drugs. Assumption of the upright position is also important. Other chest pains were due to trapping of an air bubble in the esophagus, congestion, carcinoma and peptic ulcer. In a patient already known to have heart disease, anxiety may be great, and a true explanation of the patient's discomfort is desirable.—*Clinical Aspects of Pain in the Chest: II. Pain Arising from the Esophagus*, T. R. Harrison, *Am. J. M. Sc.*, June, 1945, 209: 765.—(G. F. Mitchell)

Thoracic Wounds.—Principles of treatment of thoracic wounds, based on 1,000 casualties seen in the European Theatre, are applicable to civilian practice. Shock in thoracic wounds is usually initiated and perpetuated by cardio-respiratory disturbances and persisting pain; hemorrhage is often of only secondary consideration. Pain, from contusion of soft tissues or fractured ribs, is well controlled by 5 cc. of 1 per cent procaine injected into each involved costal nerve, either locally, regionally (at the angles of the ribs) or paravertebrally. Trauma to the lung produces diffuse interalveolar and interstitial hemorrhage, localized edema and probably increased secretion from the bronchial mucous glands—"the traumatic wet lung syndrome." Treatment is directed toward improving the bronchopulmonary drainage, as danger of asphyxiation is present in such patients. Carbon dioxide and oxygen may be used, coughing is urged and mechanical aspiration is indicated if the foregoing measures do not produce drainage of the secretions. For the latter, a tracheobronchial catheter used without anesthesia is recommended. Transpleural approach to heart wounds is preferred where cardiac contusion is suspected. Pressure pneumothorax is best treated by use of a mushroom type catheter, of larger gauge than the rent in the lung, attached to a water trap. Early and repeated aspirations of hemothorax is the treatment of choice; there is no evidence that this increases the bleeding and actually fewer infections developed in aspirated chests. Only about 10 per cent of the hemothoraces clotted, forming an organization from proliferation of fibroblasts and angioblasts from both the visceral and parietal pleural surfaces. A firm peel of fibroblastic membrane 1 cm. or greater in thickness may eventually form, producing roentgenographic evidence of a generalized hazy chest and/or retraction of intercostal spaces, poor expansion, diffuse thoracic pain or dyspnea. In such cases it is of importance to recognize that there is no thickening of the visceral pleura, whether or not the hemo-organization was associated with infection. About six weeks after injury, decortication (removal of the peel) may be performed through a posterior or posterolateral thoracotomy incision. For infected hemothorax, if small, simple drainage was usually satisfactory; total hemothoracic empyema with more than 25 per cent collapse

of the lung was treated by early decortication.
—A Review of Certain Principles in the Management of Thoracic War Wounds: Their Application to Civilian Practice, P. C. Samson, California & West. Med., Tuberc. Supp., August, 1946, 65: 25.—(P. Q. Edwards)

Circulation in Penetrating Chest Wounds.—Quantitative hemodynamic data on 13 patients with chest injuries are presented. Four of these patients had no evidence of circulatory difficulties while 9 of them did. The studies on those without circulatory difficulty gave values which were similar to those on normal subjects. The 9 patients who had circulatory insufficiency showed hypotension, a low peripheral resistance, a relatively normal cardiac output, and a normal right atrial pressure. A group of patients who had circulatory insufficiency following acute hemorrhage showed hypotension, an increased peripheral resistance, a low cardiac output and a low right atrial pressure. The circulatory failure in these patients with penetrating wounds of the pleura appeared to be primarily the result of arteriolar dilatation. It is believed that the arteriolar dilatation is reflex in origin and it is suggested that the afferent impulses may arise in the pleura. (Authors' Summary)—*The Circulation in Penetrating Wounds of the Chest: A Study by the Method of Right Heart Catheterization*, A. J. Merrill, J. V. Warren, E. A. Stead, Jr. & E. S. Brannon, Am. Heart J., April, 1946, 31: 418.—(G. C. Leiner)

Nerve Block in Treatment of Thoracic Injuries.—The great value and simplicity of nerve block to control pain in all types of chest injuries is stressed. With relief of pain patients respond better to shock therapy, and withstand transportation better. Nerve block is more physiological and far more efficient than chest strapping because strapping favors anoxia and retention of bronchial secretions by limiting pulmonary expansion and interfering with the cough mechanism. Chest strapping is necessary in those with a

severe degree of "flail" chest on account of the persistence of paradoxical chest motion. Nerve block is particularly useful in treatment of traumatic wet lung syndrome. Intercostal nerve block because of its simplicity is used as frequently as possible. In uncontaminated wounds local infiltration of procaine at site of injury is satisfactory. If these two methods are unsatisfactory or cannot be used, a paravertebral sympathetic block should be done. If the injury is located so posteriorly that site of injection is contaminated, a paravertebral block of two nerve segments above this area will be of considerable value in blocking pain impulses. Relief of pain following nerve block persists for several hours at least, but as a rule persistent relief follows one effective block. It is rare that more than three consecutive blocks are required. The techniques of both types of nerve block are given and illustrative cases cited.—*Nerve Block in the Treatment of Thoracic Injuries*, Major L. J. Fitzpatrick & Captain A. J. Adams, J. Thoracic Surg., December, 1945, 14: 450.—(W. M. G. Jones)

Chest Wounds.—The most important object in treatment of injuries involving the pleura is early pulmonary reexpansion, since by this means pleural infection is limited and respiratory efficiency restored. The prognosis of penetrating wounds is influenced as much by the condition of the lung as by that of the pleura. Expansion of the lung is slower after penetrating wounds than after non-penetrating injuries, quite apart from infection. It is suggested that in most cases this difference is due to pulmonary injury which is not always recognized, and that treatment directed to the pleura alone therefore will not always result in reexpansion of the lung. The presence of pneumothorax is an unfavorable influence and greatly increases the chances of pleural infection. Elimination of the pleural space is of such significance that it is reasonable to regard early pulmonary reexpansion as even more important than avoidance of infection, first, because the former is a most useful means of

promoting the latter, and, secondly, because the prognosis of localized basal empyema is much better than that of persistent total hemopneumothorax, even if this remains sterile. Decision on the need for operation is often difficult. As a general rule it can be said that if a penetrating wound is larger than about 1 cm. it will probably need operation. If there is a pneumothorax as well, the necessity for surgery is almost certain. Treatment for small penetrating wounds is by aspiration of hemothorax and instillation of intrapleural penicillin. If aspiration fails to eliminate hemothorax within two weeks, surgical evacuation must be considered. The prognosis of persistent apical hemothorax, because pulmonary efficiency is very much worse than that of basal hemothorax, because of the collapse of the lung at the apex than at the base. In almost every case of hemothorax in which the lung does not reexpand easily it will be found that there has been penetration or perforation of the pulmonary tissue by the missile. It is common experience that in the presence of partial bronchial obstruction due to any pathological process, initiation of pneumothorax will often precipitate total atelectasis, which is difficult of resolution. Hemorrhage into the lung after injury might be expected, owing to interference with the air-passages, to show this lethargy in reexpansion in the presence of a pneumothorax. In surgical treatment an important factor is suction, using an apical and basal catheter with subatmospheric pressure. In the author's series the rate of infection of hemothorax following penetrating and perforating wounds was less than 14 per cent.—*Indications for Surgery in Penetrating Wounds of the Chest: The Importance of Pulmonary Injury*, G. Quist, *Brit. M. J.*, October 20, 1945, 2: 521.—(D. H. Cohen)

Cor Pulmonale.—Sixty consecutive cases of cor pulmonale unassociated with other forms of heart disease were studied at necropsy. Only those cases were selected in which the thickness of the right ventricle

averaged over 5 mm. and in which the walls of the right ventricle were hypertrophied to a greater degree than those of the left ventricle. Etiological factors were pulmonary emphysema in 40 cases, bronchiectasis in 6, pulmonary asthma in 6, silicotuberculosis in 3, pulmonary tuberculosis in 2, kyphoscoliosis, pulmonary arteriolar sclerosis, organized pulmonary thrombi, each in one case. There were 56 men and 4 women. The peak age incidence was between 50 and 65 years. Only one of the 40 patients with emphysema was a woman. The pulmonary arteriolar sclerosis found in some of these cases was not extensive enough to cause the cardiac changes; the same was true for pulmonary fibrosis which was present in only 16 out of the 40 cases with emphysema. Diffuse obstructive emphysema, either primary or secondary to such disease as pulmonary tuberculosis or silicosis, was considered to be the significant underlying pulmonary factor in the majority of the cases. Diffuse obstructive emphysema was thought to produce a changed pressure relation within the alveoli and in this manner result in an increased resistance to the flow of blood to the lungs. This was considered to be the primary mechanism in the development of cor pulmonale. Polycythemia, pulmonary arteriolar sclerosis, fibrosis, bronchopulmonary arterial shunts probably play a secondary rôle. The weight of the hearts was between 350 and 770 g., the average being 460 g. The thickness of the wall of the right ventricle was between 0.6 cm. and 1.4 cm., the average being 0.8 cm. In some cases there was also hypertrophy of the left ventricle wall, possibly due to anoxemia. Inflammatory changes in the bronchi were found in 75 per cent of the cases of diffuse obstructive emphysema. In 7 patients the chief initial complaint was precordial pain, possibly due to myocardial anoxemia; none of these showed coronary sclerosis or myocardial fibrosis of significant degree. Clubbed fingers were seen in 19 of the 60 patients. Polycythemia was found in 14 of 39 cases in which blood counts were made. Roentgenological

evidence of cor pulmonale was hidden in most cases by the alterations in the chest created by emphysema, fibrosis, pleural obliteration or kyphoscoliosis. In 14 of the 21 cases in whom electrocardiograms were taken there was right axis deviation. The most common error in diagnosis was: arteriosclerotic heart disease, which diagnosis was made in 26 cases. The diagnosis of cor pulmonale was in no case made prior to the onset of cardiac failure.—*Chronic Cor Pulmonale: Sixty Cases Studied at Necropsy, D. M. Spain & B. J. Handler, Arch. Int. Med., January, 1946, 77: 87.*—(G. C. Leiner)

Aneurysm of Innominate Artery.—Fewer than 100 operations have been performed on the innominate artery since 1818; approximately 25 per cent have been for aneurysm. In all, there have been 23 ligations for innominate aneurysm. The procedure is very hazardous, secondary hemorrhage being the chief cause of death. The author reports a case in which the cause was syphilis and which first appeared after a severe coughing spell. The aneurysm was ligated proximally by means of two wide rubber bands. Pulsations ceased immediately. There were no brachial or cerebral complications. Eventually the mass completely disappeared.—*Ligation of the Innominate Artery for Innominate Aneurysm Using Rubber Bands, J. C. Trent, Surg., Gynec. & Obst., April, 1946, 82: 463.*—(A. G. Cohen)

Erythema Nodosum.—Among 40 cases of erythema nodosum observed by the author, only 33 had positive tuberculin reactions. Of these 33, 6 had certain clinical tuberculosis. In the remaining 27, tuberculosis is the most likely etiological disease, although some patients presented a picture of acute polyarthritis which is not often seen in tuberculosis. Concerning the 7 tuberculin-negative patients, no etiological factor could be demonstrated in 5. Four of these 5 patients had acute polyarthritis, and the fifth had a sore throat and nephritis. It would thus appear that the accompanying erythema nodosum may have been of rheumatic origin. One

patient developed manifest signs of congenital syphilis shortly after her erythema nodosum, and the other case was very suspicious of sarcoidosis, although erythema nodosum is ordinarily not seen in sarcoidosis. The presence of lymph node enlargement in the mediastinum does not appear to clinch the diagnosis of tuberculosis even in a tuberculin-positive case. Enlarged hilar nodes were observed in 3 out of the 7 cases of tuberculin-negative erythema nodosum. It is possible, therefore, that the tuberculin-positive patients who had evidence of polyarthritis have a rheumatic etiology as the basis for their disease. The symptom complex of sore throat, erythema nodosum, polyarthritis and unilateral or bilateral mediastinal node enlargement may, then, be more often rheumatic than tuberculous.—*Tuberculin Negative Erythema Nodosum, J. H. Vogt, Acta. med. Scandinav., January 21, 1946, 123: 161.*—(H. Marcus)

Pericarditis following Upper Respiratory Infection.—Eight case reports of patients with acute pericarditis with effusion are presented. Six of these patients had a history of tonsillitis, pharyngitis or nasopharyngitis; the remaining 2 patients had a nonproductive cough. The main symptom was substernal pain in all cases. A precordial friction rub was heard in 5 patients. The highest leukocyte counts were between 6,000 and 27,400 per cubic millimeter. Pericardiocentesis was done in 5 cases; hemorrhagic fluid was obtained in 4, clear amber fluid in one. Bacteriological examination was negative in all cases. Electrocardiographic findings were: Progressive inversion of the T waves, straightening of the S-T segments, elevation of the S-T segments. Two possibilities of the pathogenesis are considered: "(1) The proximity of the hilum lymph nodes with extension of the infection into the pericardial sac. (2) A hypersensitive response by the pericardium to an offending organism in which the immune reaction of the body is inadequate."—*Pericarditis with Effusion following Infections of the Upper Respiratory Tract, D. A. Nathan & R. A.*

Datke, Am. Heart J., February, 1946, 31: 115.—(G. C. Leiner)

Klebsiella Pneumoniae Bacteremia.—Infections with *Klebsiella pneumoniae* have always been regarded as serious, fatality figures varying between 35 to 97 per cent. Later figures are somewhat lower, possibly due to aid from sulfadiazine or sulfapyridine, for experimental studies of the effects of these drugs on animals suggest that they may actually exert some curative effect. However, with a fatality still of 75 to 85 per cent, any therapy promising aid should be given adequate trial. The use of the new antibiotics has undergone radical modifications and the initial concepts in dosage have been revised with consequent changes in the reported effectiveness of the drugs. There has also developed marked variation in methods of administration frequency of dosage and other features. It long was customary to classify bacterial response to therapy in accordance with the organism's staining qualities. Now again we find bacteria being segregated in accordance with this thesis, while the staining property of bacteria neither confers pathogenicity on them nor does it affect their vulnerability. Hence, it is felt that some suspicion must be held for the precepts in which all gram-negative bacilli are listed as "insusceptible" to penicillin including the *Klebsiella pneumoniae*. It, therefore, seems desirable to present a case of *Klebsiella* bacteremia treated with penicillin with dramatic results. A seaman was admitted to a U. S. N. Base Hospital in the South Pacific in deep coma, with a high temperature, uneven rasping rapid respiration, and who, on initial examination, was found to have a purulent nasal discharge, a left pharyngeal abscess, diffusely red throat and all other findings essentially negative. The blood count revealed 34,000 white cells with 86 per cent polymorphonuclears. On attempting to aspirate a specimen of gastric contents the pharyngeal abscess ruptured and drained. Blood culture was taken and 5.0 g. of sodium sulfadiazine given intravenously. The temperature rose

to 105.4°F (r), respirations were 36, pulse 150. Ophthalmoscopic examination revealed haziness of both nasal disc margins. Penicillin was begun in 5 per cent glucose by continuous intravenous drip, the patient receiving 300,000 units in twenty-four hours. The following day the blood culture was reported as containing *Klebsiella pneumoniae*. There was elevation of the left optic disc and haziness of the nasal disc border on the right, and an early cavernous sinus phlebitis was suspected. The patient's condition was desperate, and it was decided to continue full doses of penicillin. During the two following days continuous oxygen was also employed, and sedation was required to control extreme restlessness. The third day the temperature, pulse rate and respirations decreased steadily (99.8°F.), and the patient responded to stimuli. A productive cough was present, and an X-ray film at this time revealed a small area of consolidation at the left base. On the fourth day the penicillin was given intramuscularly, and the optic nerve heads appeared normal. While some cases of *Klebsiella* bacteremia are not fatal, especially if there is an accessible primary focus, the extremely rapid cessation of symptoms in a patient so critically ill inclines one strongly to the conclusion that the therapy had a marked effect. A blood culture taken on the second day of penicillin therapy was negative. It must be remembered that penicillin exerts its action as a bacteriostatic only during bacterial multiplication. It is not unreasonable to believe that bacteriostasis may reveal itself *in vivo* to be a critical factor though the noted changes *in vitro* were insignificant. It is hoped that this report will encourage further trial of penicillin in large doses in future *Klebsiella pneumoniae* infections.—*Klebsiella Pneumoniae Bacteremia Successfully Treated by Penicillin*, J. L. Kobacker & G. B. Mehlin, Am. J. M. Sc., July, 1945, 210: 66.—(G. F. Mitchell)

Recovery from Hemolytic *Staphylococcus Aureus* Bacteremia.—(This case is of historical interest because it was the first case of this kind in the Mediterranean theater.

Due to delay incident to war, it was received for publication one and one-half years after it was written.) This is a case report of a soldier wounded in the right chest by high explosive fragment on July 19, 1943. Wound was debrided and he was evacuated to the rear. Five days later a thoracotomy was done and the fragment and clot removed. No sulfa drug was used, and incision closed with water seal drainage. Five days later frank pus was found in the wound, which was opened and drained. Cultures revealed hemolytic staphylococcus aureus. The next day patient developed embolic foci in the good lung, in spleen and in tips of extremities. Blood culture was positive. Full doses of sodium sulfathiazole and daily blood transfusions were used for seven days without benefit. On August 17 his condition was rapidly deteriorating. Sulfathiazole and blood transfusions were stopped and penicillin begun. He received 50,000 units intravenously twice with a six-hour interval, then 25,000 units also intravenously, and thereafter 15,000 units intramuscularly every three hours. There was an immediate response and in forty-eight hours spontaneous subsidence of all the infected emboli. By August 27 the blood cultures were negative, despite a three-day discontinuance of treatment due to lack of drug, and penicillin was stopped August 31. Patient was followed and made uninterrupted recovery.—*Recovery from Hemolytic Staphylococcus Aureus Bacteremia Attributed to Penicillin Therapy*, Major T. H. Buford, Major P. C. Samson, Major L. A. Brewer, III & Major B. Burbank, *J. Thoracic Surg.*, December, 1945, 14: 488.—(W. M. G. Jones)

Anal Fistula.—Six hundred patients with anal fistulae were studied in an attempt to evaluate the part tuberculosis plays in the etiology of anal fistulae. Clinical and histological examinations and guinea pig inoculation were used to determine the nature of a fistula. In 88.5 per cent of the 600 cases no evidence of tuberculosis was found anywhere, neither in the body nor in the fistula. In

5.5 per cent there was evidence of tuberculosis somewhere in the body in addition to positive histological findings and guinea pig inoculations. In 3.2 per cent no evidence of tuberculosis could be found in the fistula but there was clinical and roentgenological evidence of tuberculous infection somewhere in the body. In one per cent there was clinical and roentgenological evidence of tuberculosis somewhere in the body but only the guinea pig inoculation from the anal fistula was positive. In 1.8 per cent either histological examination or guinea pig inoculation or both tests were positive in the absence of demonstrable tuberculous disease at any other site.—*Tuberculosis and Anal Fistula*, R. J. Jackman & L. A. Buic, *J. A. M. A.*, March 9, 1946, 130: 680.—(H. Abeles)

Anaphylactic Reactions to Congo Red.—In 100 consecutive congo red tests, 6 instances of severe reactions, including 2 deaths, were recorded. Minor reactions, such as chills and dizziness, have not been seen uncommonly among clinicians, and even the more severe reactions may not be too rare, although no cases of death have heretofore been published. The cause of such reactions is not clear: perhaps they are related in some way to the hemostatic properties attributed to congo red, or, more likely, a sensitization phenomenon is responsible, in so far as all patients manifesting severe reactions had been given congo red injections previously without reaction. Although congo red is not a protein, the dye, coupled with proteins of his own serum, may form an azoprotein which, being foreign to the patient, sensitizes him, so that he reacts to a subsequent injection by anaphylactic shock. Caution must therefore be used in injecting congo red into patients already tested with the dye on some former occasion. The 6 case histories are reported in detail.—*Systemic Reactions to the Intravenous Administration of Congo Red*, I. J. Schikoff & I. J. Bernstein, *Quart. Bull. Sea View Hosp.*, April, 1946, 8: 181.—(P. Q. Edwards)

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Controversial Points in Antituberculosis Work.—Some controversial issues of basic importance are presented and briefly discussed. One is the proper use and dosage of tuberculin in mass surveys and diagnosis. Another is the question whether or not children with tubercle bacilli in gastric lavage, following treatment, may be permitted to attend school. Whether and where BCG vaccination should be used is still *sub judice*. It is pointed out that observations on more than 15,000 student nurses indicate that the first few years following tuberculin conversion are the most critical ones for the development of clinical tuberculosis (a conclusion which most Scandinavian authors reached years ago). This question can be answered for the U. S. only by the proper use of tuberculin tests and by serial examinations over many years.—*Controversial Issues in Tuberculosis Control* (Editorial), H. E. Hilleboe, *Pub. Health Rep.*, November 1, 1946, 61: 1561.—(M. Pinner)

Tuberculosis Association Programs.—Since morbidity and mortality from tuberculosis have sharply diminished in recent years and the income of the National Tuberculosis Association from Christmas seals has increased, Dublin urges that the program of the Association be broadened to include other public health activities while at the same time intensifying and perfecting its endeavors for the eradication of tuberculosis.—*The Trend of Tuberculosis Association Programs*, L. I. Dublin, *Am. J. Pub. Health*, October, 1946, 36: 1105.—(M. B. Lurie)

Principles of Tuberculosis Control in Minneapolis.—The principles of the antituberculosis work in Minneapolis, which have been in use for the last twenty-six years, are described and discussed in some detail. The main factors were methodical tuberculin and X-ray surveys, isolation of contagious cases, and prompt treatment of patients with active disease. During these twenty-six years, tuberculosis has rapidly declined in Minneapolis, as shown by a decrease of the mortality rate from 120 in 1920 to 27.1 in 1945, a decrease in tuberculin reactors among grade school children from nearly 50 per cent in 1926 to about 8 per cent in 1944, a decrease of the annual infection attack rate among young children from 3.5 per cent in 1926 to 0.003 per cent in 1944 and a decline in mortality of children during the first five years of life from a high rate in the 1920's to not a single death from tuberculosis in 1945.—*The Establishment and Use of Fundamental Procedures in Tuberculosis Control*, J. A. Myers, *Pub. Health Rep.*, November 1, 1946, 61: 1563.—(M. Pinner)

Tuberculosis in Newfoundland.—The tuberculosis mortality in Newfoundland is several times that in England or Canada. The incidence of active pulmonary tuberculosis is between 3 and 4 per cent, more than three times the incidence in England. More than half of the deaths from disease between the ages of 15 and 45 were ascribed to tuberculosis. The mortality from tuberculosis in Newfoundland is greater among females than among males. Despite defects in available statistical evidence, collation of a number of

studies indicate the seriousness of the tuberculosis situation. Factors responsible for the high incidence include poverty, poor nutrition, ignorance, fatigue and especially excessive exposure due to late diagnosis and lack of institutional accommodations. Improved standards of living, especially of housing and nutrition, are urged to raise the resistance of the general population to the tubercle bacillus, but BCG vaccination is not mentioned. Dispensaries, laboratory service, X-ray and specialists to examine suspects, contacts, both of known cases and of tuberculin reacting children, and adult groups of other kinds, are recommended for the identification of potential and actual sources of infection and of cases that might benefit from treatment. Increase in the institutional accommodation for patients from the present 350, which is only 0.75 beds per annual death, is essential, but home care may be improved in the meantime. Social measures to assist the patient and his family, by financial allowances and other forms of social help, and a campaign of public health education and provision of increased medical and nursing personnel are recommended.—*1945 Tuberculosis in Newfoundland, T. O. Garland & P. D'Arcy Hart, Report of a five weeks' visit, Privately printed.*—(E. Bogen)

Chest Examinations in Discharged Soldiers.

—This is an abstract from a paper by W. W. Lindahl, "Pulmonary Tuberculosis and Other Thoracic Diseases Among Army Separates." Routine chest photo-roentgenograms were taken of 93,500 soldiers at a Separation Center. There was evidence of tuberculosis in 122 (0.13 per cent). In 50 of these cases the lesions were found to be inactive. There were cavities in 10, and pleural effusion was present in 4; 35 cases of pneumonia and 4 cases of thoracic tumors were detected. The low incidence of thoracic diseases in separates may be due to the induction screening and medical supervision of the troops.—*Thoracic Diseases among Separates, (Not signed), Bull. U. S. Army. M. Dept., November, 1946, 6: 544.*—(O. Pinner)

Pulmonary Tuberculosis in Medical Students.—The prevalence of significant adult type pulmonary tuberculosis among Harvard medical students was 2.2 per cent. Slightly more than 30 per cent of students entering school as nonreactors became reactors before graduation. Conversion from a nonreactive to a reactive state (to tuberculin) while in medical school carried a liability of more than 5 per cent that the disease would develop before graduation. The number of cases of pulmonary tuberculosis developing in the last two years of school was four times as great as those occurring in the first two years. However, the incidence of acquisition of tuberculous infection, as indicated by the tuberculin test, was approximately the same (12 to 13 per cent) for each year. This indicates that other factors than the opportunity for infection contribute to the development of clinical tuberculosis. The disease often became symptomatic between annual examinations, indicating the rapid progression of lesions, once they have appeared. It is felt that an interval of one year between examinations is too long. In order to detect lesions at an early stage, semi-annual examinations are required.—*Pulmonary Tuberculosis in Harvard Medical Students, H. P. Brean & L. W. Kane, New England J. Med., September 5, 1946, 235: 315.*—(A. G. Cohen)

Fluoroscopy in Railroad Employees.—Routine fluoroscopy was carried out on 56,541 employees of the *Société Nationale de Chemins de Fer Français*; 13,249 of these were reexamined one to two years later. Initial examination: normal findings were recorded in 83.9 per cent of cases, abnormal findings in 16.06 per cent (9,088 cases). The classification of the abnormal findings was as follows: negligible pulmonary or pleural anomalies 13.04 per cent, cases of known pulmonary tuberculosis 0.74 per cent, cases of pulmonary tuberculosis picked up by the routine examination and confirmed bacteriologically 0.23 per cent, active pulmonary tuberculosis with negative sputum 0.02 per cent, pleural and pul-

monary lesions necessitating supervision 0.49 per cent, nontuberculous disease 1.54 per cent. The prevalence of previously unknown active pulmonary tuberculosis with positive sputum was 2.28 per cent of all persons examined. The lowest prevalence of previously undiagnosed tuberculosis was found between the ages of 15 and 25. Most cases were found in the age-group between 25 and 50. Among the 129 cases with positive sputum 40 per cent showed bilateral disease. Cavities were demonstrable in 52 per cent of cases. One hundred and seventeen of the 129 cases of open pulmonary tuberculosis could be followed for four years. Review of the results at the end of that time showed that 52 per cent had returned to work and 22 per cent had died. There were 13,249 employees who underwent a second examination one to two years after the initial examination. The prevalence of newly discovered cases with positive sputum was 0.6 per cent (as compared with 2.3 per cent at the initial examination). The incidence varied according to the time elapsed since initial examination.—*Résultats immédiats et éloignés d'examen radiologiques systématiques intéressant le personnel de la Société Nationale de Chemins de Fer Français, (région de l'est), A. Biedermann, A. Alibert, J. Mery, M. Lerolle & P. Paillas, Rev. de la tuberc., 1946, 10: 97.*—(V. Leites)

Tuberculosis in Prostitutes.—In 1941 an X-ray survey was conducted in Rio de Janeiro on 1,684 prostitutes; 36 cases of active pulmonary tuberculosis were discovered, including 4 cases of miliary tuberculosis, 4 cases of apical tuberculosis, 2 cases of pleural tuberculosis, 5 cases of ulcero-fibrotic lesions and 21 cases of ulcero-caseous lesions. Mass surveys of the chest should be extended to the totality of the population and should be periodically repeated. The average duration of the "silent phase" of pulmonary tuberculosis is estimated at three years. The distinction currently made between tuberculous infection and tuberculous disease is no longer justified in the light of the knowledge accumulated during

extensive roentgenological surveys. Each individual with tuberculous infection is a potential candidate for tuberculous disease.—*Tuberculosis inaparente, A. de Paula, Prensa méd. argent., August, 1946, 33: 1571 and 1721.*—(L. Molnar)

Abnormal X-ray Findings in Surveys.—A new and elaborate classification is presented of persons with abnormal pulmonary X-ray findings, as a guide for the practitioner, indicating minimum standards for further observations and final disposition of such persons. Since the main part of this paper is a tabulation, it is not suitable for detailed abstracting.—*Guide for Disposition of Persons with Abnormal Pulmonary Findings on X-ray Films, H. E. Hilleboe, Pub. Health Rep., December 6, 1946, 61: 1759.*—(M. Pinner)

Photofluorographic Survey.—Approximately one-half of the population (32,825 persons) of the French town of Montreuil could be persuaded to submit to photofluorographie examination. One hundred per cent of the children were included in this survey; 38.2 per cent of the male population and 48.2 per cent of the female population responded. The percentage of participants was much higher in the economically better situated groups. The incidence of active tuberculous disease, previously undiagnosed, was 0.27 per cent. In an additional 0.37 per cent of cases tuberculous lesions of undetermined activity or of a definitely inactive character were found. Non-tuberculous disease was found in 0.08 per cent.—*Le bilan de l'expérience de Montreuil-sous-Bois: radiophotographie systématique de toute la population d'une ville française, M. Fourestier, Rev. de la tuberc., 1946, 10: 54.*—(V. Leites)

Stereoscopy.—Stereoscopy may be of considerable assistance in the detection of an abnormal condition and the identification of the disease. It will exhibit its greatest usefulness in mass radiography in those cases in which an existing lesion is so small it may

be hidden by a rib or the clavicle. Recently over 4,000 stereoscopic 4 x 10 cm. films were examined to determine the number of minimal tuberculosis lesions that might be overlooked if single films had been made in mass chest surveys. The group, obtained from several surveys, included a large number of pathological lesions. Six hundred and nine of the group presented evidence of minimal tuberculosis. A little more than one-third of these exhibited lesions considered worthy of further clinical investigation. This ratio of significant to nonsignificant cases is in close agreement with mass case-finding work throughout the United States. In this group of potentially significant films only 7 showed lesions visible in one of the stereoscopic views not seen in the other or 1.1 per cent of the films showing minimal tuberculosis. In 27 other films the lesions were seen to better advantage on one of the stereoscopic pair. Mass chest surveys by the United States Public Health Service and associated groups have shown that approximately one per cent of the population has X-ray evidence of minimal tuberculosis. Thus, one may expect stereoscopy to be of help in only 6 per 100,000 persons examined. This is an insignificant number, especially in view of the personal error of the physician reading the chest films. Since the cost is almost double, the case-finding dollar will go only half as far, thus reducing the number of persons examined and the number of cases of tuberculosis found. It would seem desirable, therefore, that the single film be used for the detection of disease and the stereoscopy confined to the identification of the lesions discovered by mass radiography.—*The Value of Stereoscopy in Mass Radiography*, I. Lewis & R. H. Morgan, *Radiology*, February, 1946, 46: 171.—(G. F. Mitchell)

Fluoroscopic Screens.—This is a highly technical discussion of the factors responsible for the persistence of luminescence in fluoroscopic screens.—*The Persistence of Fluoroscopic Screens*, W. W. Van Allen, *Pub. Health Rep.*, November 1, 1946, 61: 1588.—(M. Pinner)

Primary Tuberculosis in Adults.—The dogma of universal tuberculous infection in childhood is no longer true. In most places, the greatest amount of tuberculous infection now occurs after school age. Primary infections in later years are not rare and some individuals escape infection altogether. Approximately one-third, occasionally one-half, of the primary infections are accompanied by demonstrable roentgenographic findings, such as hilar adenitis, serous pleurisy, relatively extensive infiltration of the lung, perihilar infiltration and hematogenous dissemination. There appears to be little difference in the immediate reaction between adults and children, except that hematogenous dissemination is more frequent and hilar adenitis and perihilar infiltration are more marked in children. Destructive pulmonary tuberculosis rarely occurs in childhood. The greatest number of cases and of deaths occurs between the ages of 15 and 30. There is no justification for distinguishing between "childhood type" and "adult type." In Norway, the term "reinfection type" is used only in reference to cases of new infection where the original infection is completely extinguished; such cases are very rare. A new infection in an organism where the old infection is still living is designated "superinfection." The time interval between the primary infection and destructive pulmonary tuberculosis is now known to be quite short in most cases; it is generally under five years, often only from one to two years. This has been ascertained by the wide-spread use of tuberculin testing and by using erythema nodosum as the basis for determining the time of infection. Pleurisy most often appears within six months after infection and large numbers of cases of pulmonary tuberculosis follow this manifestation within a few years. There is a wide diversity of opinion on the question of the pathogenetic connection between the manifestations of the primary infection and those of destructive pulmonary tuberculosis. Evidence from pathological anatomy is unsatisfactory and information must be derived from clinical and radiographic data. The conclusions of German investigators that

the subapical *Frühinfiltrat* represented super-infections were formed without regard to the tuberculin reaction. Recent evidence indicates that these *Frühinfiltrate* may well represent primary infections, leading to the further conclusion that destructive pulmonary tuberculosis develops in some cases from a direct breakdown in the area of the primary focus. In other cases, a quiescent primary focus can be reactivated after a long interval. In still other cases, there is evidence that the destructive process begins in an entirely new infiltration at another site. There are thus four different possibilities in pathogenesis: (1) direct development from the primary lesion or its immediate surroundings; (2) reactivation of latent primary foci; (3) metastatic foci of either hematogenous, lymphogenous or bronchogenic origin; and (4) new foci caused by superinfection. It is very likely that the two latter types are of much less importance than the two first ones. Little importance is attached to superinfection in the question of health and disease. Age, heredity and environment are the leading factors in the prognosis of a primary infection. —*The Relationship between Primary and Adult Tuberculosis*, H. J. Ustvedt, *Brit. J. Tuberc.*, July, 1946, 40: 85.—(A. G. Cohen)

Primary Tuberculosis in Adults.—Most serious, frequently fatal, pulmonary tuberculosis developing directly after primary infection in an adult belong to the primary or secondary stages of the disease, rather than to the common tertiary stage of Ranke. They progress by primary excavation, by rupture of lymph nodes with consequent bronchopneumonic spread, or by miliary or hematogenous dissemination, similar to the course described in infants. Only occasionally, after a short secondary stage, does the patient arrive at the tertiary stage and present an early localized infiltration. —*Les primo-infections tuberculeuses malignes de l'adulte*, A. Dufourt, *Presse méd.*, August 31, 1946, 54: 558.—(E. Bogen)

Primary Tuberculosis in Adults.—Routine X-ray examinations and tuberculin tests

were carried out on 2,873 young adults (university students, college students and employees of the Ukrainian Tuberculosis Institute). The period of observation ranged from seven months to four years. Two hundred forty-three persons were found tuberculin-negative on initial examination (Mantoux 1:100). In these cases X-ray films and tuberculin tests were repeated at intervals of three months; 92 cases developed positive tuberculin reactions while under observation. Six employees of the tuberculosis institute were found to be tuberculin-negative; they all showed a conversion to a positive reaction within a period of six months. Out of the 243 cases with negative tuberculin reaction, 31 (12.8 per cent) developed active tuberculosis. Among the 2,630 positive tuberculin reactors only 51 (1.9 per cent) developed active tuberculosis while under observation. Among the 31 active primary forms there were 6 cases of primary complex, 8 cases of hilar adenopathy, 13 cases of exudative pleurisy (42 per cent), 3 cases of limited micronodular dissemination in an upper lobe, and one case of bilateral extensive dissemination. The course was benign in most cases. The diagnosis of primary tuberculosis in these cases was based on the observation of a preceding conversion of a negative into a positive tuberculin reaction. Among the 51 cases of active tuberculosis having developed in the group of positive tuberculin reactors a low incidence of exudative pleurisy was noted in contradistinction to the group with primary infection. There was a higher incidence of unilateral disseminated forms. —*Early Forms of Primary Tuberculosis in the Adult*, G. S. Ginsburg, *Probl. tuberk.*, 1946, No. 1, 3.—(V. Leites)

Primary Infection.—Comparison of statistical data demonstrates an increase in the incidence of primary infection in contacts during the war; 401 contacts, having a source case in the family, were tuberculin-tested in 1944. The total percentage of tuberculin reactors was 75.06 per cent, as compared to 64.74 per cent, in a similar group in 1940. The increase was particularly evident in the

age group 13 to 15 with an incidence of 54.54 per cent tuberculin reactions in 1940 and 83.82 per cent in 1944. Similarly the incidence of positive reactions at the age of 2 showed an increase from 50 per cent to 66.6 per cent.—*Contribution à l'étude de la primo-infection dans la famille du tuberculeux*, H. van den Eeckhout, *Rev. de la tuberc.*, 1946, 10: 18.—(V. Leites)

Chronic Epituberculosis.—Cases of chronic epituberculosis are characterized by a protracted course, long persistence of the X-ray shadows, and absence of clinical symptoms. Bronchoscopic studies revealed the following findings: in cases of epituberculosis with lobar involvement, the orifice of the lobar bronchus showed extreme narrowing due to edema and congestion of the mucosa. The opening was usually obstructed by a very tenacious and dense plug which on microscopical examination was found to consist mainly of macrophages, probably originating from the subepithelial layer of the bronchi. Tubercle bacilli were usually absent. At the stage when X-ray films showed regression of the opacity, bronchoscopy revealed a widening of the bronchial lumen. The bronchial secretions became more fluid and consisted of abundant mucus and leucocytes and a decreasing number of macrophages. The pathogenesis of epituberculosis is thus seen in a process of edema and congestion involving the lobe of the primary complex and the lobar bronchus. The narrowing of the bronchus leads to varying degrees of airlessness in the corresponding lobe. The development of congestion and edema is considered as a manifestation of a state of local hyperallergy produced by the "toxins" from the primary focus. The hypothesis attributing epituberculosis to pressure of enlarged lymph nodes on the bronchus could not be confirmed either by bronchoscopy or by tomography.—*Sur la pathogénie des épitubercules chroniques*, A. Dufourt & P. Mounier-Kuhn, *Rev. de la tuberc.*, 1946, 10: 172.—(V. Leites)

Epituberculosis.—Epituberculosis is defined as a benign form of childhood tuberculosis,

characterized by a homogeneous X-ray density and the absence of clinical symptoms. A special form of this condition, designated as "caseous-inflammatory" epituberculosis is described, in which there is cavity formation within the consolidated area. Concomitant clinical symptoms appear and the sputum becomes positive. This development is admittedly very rare, only 5 cases were found among 2,000 cases of different forms of childhood tuberculosis.—*A propos des épitubercules caséo-inflammatoires de la deuxième enfance*, M. Delord, *Le Poumon*, January-February, 1946, 2: 24.—(V. Leites)

Perforation of Tension Cavity.—Case report of a patient with bilateral cavitary disease treated with bilateral pneumothorax. After induction of the second (left) pneumothorax and consecutive pneumonolysis there was progressive ballooning of the cavity in the left upper lobe with eventual perforation and death. Autopsy showed a thin walled cavity, 4 cm. in diameter, with a round perforation on its anterior wall, measuring 1 mm. in diameter. The site of the perforation was remote from the insertion of the severed adhesions. The opening could be demonstrated by irrigating the left main bronchus, which also proved the patency of the draining bronchus in the direction towards the cavity. Its patency in the opposite direction could also be demonstrated by injection of methylene blue into the cavity through the perforation. The draining bronchus had a diameter of 3 mm.; it contained no mucous plugs and no valves. The wall revealed a few tuberculous granulations. Thus, no check-valve mechanism could apparently be invoked in this case.—*Étude anatomique d'une caverne balonnée perforée*, M. Bariéty & J. Paillas, *Rev. de la tuberc.*, 1944-45, 9: 299.—(V. Leites)

Round Foci.—Fifty patients with isolated pulmonary round foci were studied. The period of observation ranged from one to ten years. In 44 cases a single round focus was present, 6 cases showed multiple foci. Their size varied from 1 to 4 cm. in diameter.

Seventy per cent were situated in the infraclavicular area. It is believed that the round focus is usually not an early manifestation. It arises either as a perifocal pneumonic reaction at the site of an old tuberculous lesion or from a tuberculous cavity after closure of its draining bronchus. The anatomical substratum is considered to be most often a sharply circumscribed area of caseation with remnants of elastic tissue, surrounded by a thin fibrous capsule. Depending on the stage of development the lesion consists of a cheesy mass with partial softening, large accumulations of leucocytes and specific elements in the more acute cases—or in a dry brittle mass containing calcium salts, without leucocytes and specific elements in the more chronic cases. Prolonged clinical observation showed that 56 per cent of the patients had intermittently or persistently positive sputum. The course was varied. Extensive spreads and cavity formation within the round focus were observed in a considerable number of cases. Resolution of the round focus was seen very infrequently and only in fresh cases. Contraction of the foci occurred due to encapsulation and induration. It is emphasized that even in these stages reactivation and subsequent spreads are liable to occur. The prognosis of round foci is considered rather serious. Under pneumothorax treatment no resolution was observed. The favorable effect consisted in an increased induration.—*The Round Tuberculous Focus*, T. N. Oleneva, *Probl. tuberk.*, 1946, No. 1, 10.—(V. Leites)

Pulmonary and Endobronchial Tuberculosis.—The treatment of pulmonary tuberculosis in the presence of endobronchial lesions is discussed. The authors are not in favor of primary thoracoplasty. In most cases pneumothorax is not considered contraindicated *a priori*, although it is recognized that endobronchial tuberculosis decreases considerably the chances of success. The main difficulties of pneumothorax treatment in the presence of bronchial involvement are: failure of cavities to close, ballooning of cavities, perforation of cavities, development of atelectasis. It is believed, however, that pneumothorax

can be rendered more effective if combined with auxiliary measures. Good results are said to have been obtained with the puncture of ballooned cavities. Phrenic nerve paralysis in addition to pneumothorax was effective in a number of cases with endobronchial disease, where pneumothorax alone had failed. Bronchoscopic procedures are considered of the greatest importance in improving the effect of pneumothorax, especially if they precede the institution of collapse (silver nitrate application). Only if all these measures fail, should reëxpansion be attempted and thoracoplasty considered. The generally observed favorable effect of the latter on endobronchial tuberculosis is confirmed.—*Le traitement de la tuberculose pulmonaire associée à la tuberculose bronchique*, A. Dufourt, P. Mounier-Kuhn & J. Baron, *Le Poumon*, September-October, 1945, 1: 285.—(V. Leites)

Premenstrual Fever in Tuberculosis.—The study was undertaken in an attempt to elucidate the significance of premenstrual temperature in women having pulmonary tuberculosis. Fifteen normal healthy young women were used as controls. Their temperature was taken both morning and evening, for ten minutes in the mouth. This was done for at least one whole menstrual cycle. Previous studies had revealed that in the normal woman the body temperature is relatively low during the first and relatively high during the second half of the cycle. Further studies had revealed a relatively high temperature to be characteristic of the premenstrual phase and that it persisted after conception. Such a diphasic change was found in 13 of the 15 normal women studied, the temperature reached a steady maximum beginning a few days before menstruation was due. The average duration of this change was five days. The highest temperature reached was in no case above 99.0°F.; and this occurred in only one instance. In 75 per cent of cases the premenstrual temperature showed no readings above 98.4°F. Of 50 women of child-bearing age with pulmonary tuberculosis premenstrual changes occurred in 43. The reactions were of the

same types occurring in the controls. The average duration of these changes, however, was nine days instead of five, and in 53 per cent the temperature reached was 99.0°F. or over. As soon as the menstrual flow started the temperature reverted to its previous character. In 6 of these patients the characteristic changes were absent when a temporary increase of tuberculous activity occurred. During this exacerbation, shown either by a higher temperature recording or by a bigger variation in the morning and evening temperatures, the premenstrual phase invariably disappeared. One of the 43 patients possessed charts, extending over a period of five years, showing an original premenstrual rise in temperature lasting for fourteen days; now, when the degree of activity of the disease is much less, the rise lasts only for five days. In 4 patients the day preceding menstruation was marked by a sudden extreme rise in temperature. This reaction bears a strong resemblance to a tuberculin reaction. Since the symptoms complained of during the few days preceding menstruation are very similar to those of over-activity of the thyroid gland—irritability, sweating, tremor and nausea—6 patients were given thiouracil 0.6 g. daily starting two days before the expected premenstrual rise in temperature. The temperature change was eliminated and the usual concomitant symptoms were also absent. The author concludes that the normal premenstrual temperature variations are also present in patients with pulmonary tuberculosis in early, as well as advanced cases, but it tends to be more pronounced and of longer duration.—*Significance of the Premenstrual Fever in Pulmonary Tuberculosis*, R. Grenville-Mathers, *Brit. M. J.*, April 6, 1946, 1: 523.—(D. H. Cohen)

Symptoms in Pulmonary Tuberculosis.—Since the introduction of mass miniature radiography there has been a body of medical opinion, maintaining that it would be more productive of results and more economical of personnel to concentrate the use of mass radiography machines on the examination of those sections of the population presenting symptoms

suggestive of chest disease. It is generally accepted that the number of persons found by orthodox mass radiography to have significant lesions is in the region of 1.3 per cent. This figure can be subdivided into observation cases, 1.0 per cent, and treatment cases, 0.3 per cent, and it has been found that approximately two-thirds of the first group and one-half of the second group are symptom free. In order to arrive at a figure for the number of the general population having such symptoms as might be indicative of disease of the chest, a questionnaire was presented to 5,308 persons passing through a mass X-ray unit for one month. There were nine questions: (1) have you a cough of one or more months' duration; (2) any phlegm; (3) have you coughed up any blood recently; (4) have you any pain in your chest; (5) are you more short of breath than you were six months ago; (6) are you losing weight; (7) are you feeling off color or tired; (8) have you had "flu" or frequent colds recently; and (9) have you seen a doctor for any of the above complaints. It was found that the predominant symptom in men was cough (16.1 per cent) and in women lassitude (12.1 per cent), and that 36 per cent of all those interviewed presented one or more of the symptoms listed. This figure approximates very closely that for the proportion of persons found by mass radiography to have significant lesions with symptoms—thus indicating that symptoms in themselves are not likely to be of great assistance in the discovery of previously undiagnosed pulmonary tuberculosis. It should be further noted that only one-sixth of those complaining of symptoms consulted their doctor. The author concludes that it would appear that the most practical way to employ the limited number of mass miniature radiography machines at present available is on routine mass radiography during the greater part of the week, while arranging for them to be used to X-ray such groups as "symptom cases" referred to the clinic and contacts of positive cases on one afternoon a week.—*Significance of Symptoms in the Diagnosis of Pulmonary Tuberculosis*, W. P. Dick, *Brit. M. J.*, April 13, 1946, 1: 571.—(D. H. Cohen)

Bronchoscopic Treatment.—The various bronchoscopic procedures in the treatment of tuberculosis are reviewed. No major effects are attributed to simple bronchoscopic aspirations. Other manipulations, aiming at the restoration of bronchial patency, are more important and consist in removal of viscous and stagnant secretions and crusts and abrasions of endobronchial granulations and vegetations. Catheterization of the bronchi of second and third degree, in view of their dilatation, is considered with scepticism, especially in cases with organic stenosis. The possibility of releasing a visceromotor reflex by introducing a bronchial catheter is not excluded; the occasional closure of ballooned cavities after bronchoscopy is taken as a proof for such mechanism. The value of bronchoscopic treatment of endobronchial infiltrations, ulcerations and edema is questionable. Excessive repetition and too close intervals should be avoided. The traumatization inherent in many procedures may have the opposite from the desired effect, increasing the degree of obstruction by inflammation and provoking spread of infection.—*Bronchoscopio-thérapie et tuberculose pulmonaire*, A. Soulas, *Le Poumon*, May-June, 1946, 2: 173.—(V. Leites)

Cardiospasm in Tuberculosis.—In the tuberculous patient, cardiospasm is usually the result of a derangement of the vegetative nervous system; it responds well to atropine. Occasionally it has been reported that abnormal conditions of the diaphragm have given rise to cardiospasm. One patient was cured by phrenicectomy. The case reported had, in addition to cardiospasm, a fibroid tuberculous process of the upper lobe on the right, with marked shrinkage of that lobe, and displacement of the heart and upper mediastinum to the right. The combination of increased intra-esophageal pressure due to cardiospasm, and the negative pressure on the outside of the esophagus due to the fibrotic pulmonary process led to a large diverticulum which appeared on planograms as a peculiar air-containing paratracheal structure. Administration of contrast material confirmed the diagnosis.—

Kasuistischer Beitrag zum Cardiospasmus, M. Chauvet, *Schweiz. med. Wchnschr.*, November 30, 1946, 76: 1227.—(H. Marcus)

Pernicious Anemia and Tuberculosis.—The concurrence of pernicious anemia and pulmonary tuberculosis is rare. Miliary tuberculosis is a somewhat more common complication. At the Minneapolis General Hospital a recent survey revealed only one case of tuberculosis among 235 patients afflicted with pernicious anemia. This patient, a female, aged 60, had miliary tuberculosis of the bone marrow. Examination of the bone marrow had been done for confirmation of the diagnosis of pernicious anemia because of the refractory behavior of the anemic state to adequate dosage of parenteral liver extract. Pernicious anemia was confirmed, the finding of tubercles mostly of the hard type. Acid-fast bacilli were found in one large necrotic tubercle. On admission to the hospital the chest X-ray film showed a "pneumonic" process in the lower lobe of the left lung. The Mantoux test was strongly positive. A later X-ray film of the chest now showed an "apparently healed Ghon tubercle but no evidence of an active tuberculous process." Repeated examination of small amounts of sputum showed no tubercle bacilli, but several gastric washings yielded large numbers of acid-fast bacilli. Chest films taken three months after discharge from the medical service were reported as negative for tuberculosis.—*Pernicious Anemia and Miliary Tuberculosis of the Bone Marrow Organ*, E. M. Schleicher, *Am. J. Clin. Path.*, September, 1945, 15: 402.—(J. S. Woolley)

Chemistry of Chronic Lesions.—Three constituents of the tubercle bacilli were studied in an attempt to determine the agent responsible for the characteristic mononuclear cell reaction. Polysaccharides were found to produce only a transient polynuclear reaction. Extracts of the total fats in the bacilli injected subcutaneously in guinea pigs produced first a poly- then a prolonged mononuclear response,

in no way differing from the response to injection of killed whole bacilli. In comparable concentration each of the various fatty acids engendered a similar pathological reaction, suggesting a nonspecific character of the reaction. Soluble proteins, like the polysaccharides, produce a transitory polynuclear response, whereas insoluble proteins prepared by the hydrochloric acid method of Laporte, induce a mononuclear reaction indistinguishable from that produced by injection of whole bacilli. Of further significance is the demonstration that, in equivalent doses, the soluble proteins of Koch's bacilli produce mononuclear reactions much more rapidly than simple insoluble proteins, for example, horse serum proteins coagulated by heat. Conclusions seem justified that chronic tuberculous lesions are caused by at least two factors: the lipoid constituents and the insoluble proteins of the tubercle bacillus.—*Les facteurs chimiques dans la genèse des lésions tuberculeuses chroniques*, A. Delaunay, R. Vendraely & J. Pages, *Ann. Inst. Pasteur*, July-August, 1946, 72: 607.—(P. Q. Edwards)

Tubercle Bacilli in Tuberculous Lesions.—

The problem of the quantitative distribution between living and dead bacilli in tuberculous lesions is investigated. Method: two small equal fragments of a tuberculous lesion are removed; one of them is in its entirety used for inoculation on Löwenstein's medium. The number of colonies obtained is taken as an indication of the number of living bacilli at the moment of inoculation. The other fragment is divided up into slides (400 to 700), of which every twenty-fifth is stained. The number of microscopically visible bacilli in the slide is determined, which permits an estimate of the total number of bacilli in the whole fragment. Comparison is made between the number of colonies and the number of microscopically visible bacilli. Thirty-three fragments of tuberculous lesions were examined, originating from 19 cases of chronic pulmonary tuberculosis in adults and 3 cases of miliary tuberculosis in children. The possible causes of error of this method are discussed. The results are

evaluated as follows: the examination of 19 specimens did not permit to draw any definite conclusion. In 11 cases the bacillary content of the lesions was extremely low (old lesions, perifocal type of inflammation) and the least cause of error would have changed the results fundamentally. In 9 other cases the culture medium was entirely covered by colonies which did not permit the estimate of the actual number of living bacilli. In the remaining 14 cases, where a definite proportion could be established, it appeared that the number of microscopically counted bacilli was considerably higher than the number of colonies. In one case it was double in another quadruple, which is still considered within the limits of possible error. In all remaining cases, however, the proportion was 6:1, 10:1, 30:1, 50:1, 100:1, 2000:1, 3000:1, 5000:1, 10,000:1, 60,000:1. In 2 cases not one single colony was present, whereas the number of visible bacilli was 960 and 250,000 respectively. It is concluded that in many tuberculous lesions the number of dead tubercle bacilli is markedly higher than that of living bacilli. It may even happen that all visible bacillary bodies are dead. The observation is made that tuberculous lesions of a more nonspecific inflammatory character are much richer in tubercle bacilli than typically tuberculous tissue (epithelioid and giant cells). The opinion is advanced that the death of tubercle bacilli, the disintegration of their capsule with liberation of the pathogenic constituents is the origin of those processes which are considered specifically tuberculous.—*Les bacilles de Koch existants dans les lésions des phthisiques sont-ils vivants ou morts?*, G. Canetti, *Rev. de la tuberc.*, 1946, 10: 26.—(V. Leites)

Indications for Collapse Therapy.—Selection of the proper surgical procedure in a given case in which collapse therapy is indicated is of the utmost importance for good end results. While it is admitted that certain patients represent problems which do not readily fall into the main classification, most surgical cases can be classified under two main headings: (1) Thoracoplasty is advised in cases which are

relatively inactive. The process is mainly fibrotic and one or more small cavities may be present. If a large cavity is present under the same circumstances, preliminary Monaldi drainage, followed by thoracoplasty, is the treatment of choice. (2) If the process is active and progressive, with cavity formation under observation, extrapleural pneumothorax is advised. No routine procedure is performed in any given case. Thoracoplasty may be performed as a six to eight-rib upper-stage operation, or Maurer's four or five-rib operation with transposition of the scapula may be used. If preliminary Monaldi drainage is done, it is always wise to resect the anterior ribs first and institute drainage after the costectomy scar is well healed.—*Beitrag zur Kollapstherapie der Lungentuberkulose, M. Arnold, Schweiz. med. Wchnschr., November 30, 1946, 76: 1221.*—(H. Marcus)

Ballooned, Inert and Residual Cavities.—Ballooned cavities were mostly observed after collapse therapy, especially pneumothorax and pneumonolysis. The spontaneous development was either healing or perforation. Closure of the cavity is not considered infrequent and a waiting period of two months is advised before discontinuing pneumothorax. It is believed that check valve mechanism is not always sufficient to explain the ballooning process. In certain cases the intracavitary pressure is found to be atmospheric and not influenced by intracavitary insufflation and deflation. The pathogenesis is seen in a spasm of the bronchioles due to a reflex mechanism elicited from the tuberculous lesion itself or from the pleura (refill, pneumonolysis). If the diagnosis of ballooned cavity is made before institution of active therapy, an attempt at pneumothorax should be the first step, followed by pneumonolysis if necessary. Favorable results with disappearance of the ballooning mechanism were observed in one-third of such cases. Inert cavities are cavities not influenced by a good pneumothorax of several months duration. Three causes are distinguished: (1) The lack of retractability of the pericavitary lung tissue, (caseous pneu-

monia or tuberculous bronchopneumonia). (2) The cavity is situated in an area of old indurated tuberculous tissue, preventing an adequate collapse. (3) Inert cavities due to check-valve mechanism as described above. In a centrally located cavity pleural irritation with injection of gold salts is advised. Residual cavities are seen mostly after thoracoplasty and are frequently slit-like in appearance. Differential diagnosis has to be made between residual cavity and bronchiectasis or emphysematous bleb. It is believed that the incidence of residual cavitation can be reduced by using more frequently thoracoplasty with apicolysis. Additional procedures such as revision, Monaldi drainage, cavernostomy and resection should be considered.—*Les cavernes ballonées, inertes et résiduelles, R. Even & J. Lecœur, Rev. de la tuberc., 1946, 10: 109.*—(V. Leites)

Phrenic Paralysis.—This is a review of 186 cases of phrenico-exeresis performed at the Sanatorium of Huipulco from 1936 to 1944; 89 patients were males and 87 were females. The operation was performed 98 times on the right side and 88 times on the left side. One hundred and fifty-three cases presented fibro-caseous lesions, 72 of which were predominantly in the apex, 41 at the base and 40 showed extensive bilateral lesions. Thirty-four cases with exudative tuberculosis were operated on, in 17 of which the lesions were limited to the apex, in 12 to the base, and 5 patients had extensive lesions. In 87 cases phrenico-exeresis was the only surgical procedure; in 24 of these cases a pneumoperitoneum was done to complement the phrenic paralysis. In 6 cases phrenico-exeresis preceded thoracoplasty, while in 35 cases it aided the effect of pneumothorax; in 30 cases the phrenic nerve was paralyzed in addition to thoracoplasty; in 7 cases phrenico-exeresis was associated with extrapleural pneumothorax and, finally, in 14 cases it followed plombage. Roentgenological evidence of good results was obtained in 49 cases, most of them with basal lesions of a predominantly exudative character. Sputum conversion occurred in 58 cases.

Considering only the 87 cases in which the phrenic paralysis was the only surgical procedure, X-ray evidence of improvement was seen in 26 cases, mostly in those cases associated with pneumoperitoneum. Among the 92 cases of phrenico-exeresis associated with other collapse therapeutic measures the best results were seen in those with pneumothorax. Good results were obtained with phrenic paralysis following the reëxpansion of the lung after pneumothorax. These data bear out the general opinion considering the paralysis of the phrenic nerve an unreliable method, the indications and prognosis of which cannot be rationally established.—*Estudio critico de la frenicectomia, F. Rebora, Rev. mex. de tuberc., March-April, 1946, 8: 109.*—(L. Molnar)

Pneumoperitoneum with Phrenic Paralysis.—In three years' observations on 89 cases in which pneumoperitoneum had been combined with temporary or permanent phrenic paralysis, the results, verified by tomography and repeated sputum examinations, were as follows: In 58 lesions of the lower lobe, 31 successes. In 17 lesions of both lower and upper lobe, 6 healed in the lower lobe without important change in the upper lobe, one healed in both locations, 10 were without effect. In 14 diffuse lesions of the entire lung, 4 successes and 10 failures. In 7 cases with cavity in the upper lobe, only one improved. In 2 cases of draining tuberculous pleurisy, both failed. It is concluded that pneumoperitoneum aids the action of phrenic paralysis when that is indicated, which is chiefly in lesions of the lower lobes.—*Valeur du pneumopéritoine complémentaire de la paralysie opératoire du diaphragme, M. F. Magnin, Presse méd., August 31 1946, 54: 562.*—(E. Bogen)

Duration of Pneumothorax.—A change of ideas on duration of pneumothorax has taken place in French phthisiology, since Dumarest in 1929 advised indefinite maintenance of a satisfactory pneumothorax. Rist in 1930 recommended five years of effective pneumothorax treatment as safe and sufficient in most cases. Observations indicate that a great

number of patients receive refills for a longer period than five years. Among 95 such cases 15 per cent developed pleural complications after the fifth year, one-third of these complications were of a serious nature. It is felt that the theory of the necessity of a five-year treatment should at present be reconsidered for the following reasons: to-day pneumothorax is instituted earlier and for more limited lesions than in the past. The proportion of pneumothoraces improved by pneumonolysis has greatly increased. Tomography permits better observation of the lesions in the collapsed lung. The duration of pneumothorax should be adapted to each individual case and a rigid formula such as "a minimum of five years" is not justified.—*Sur la durée du pneumothorax thérapeutique intrapleurale, E. Bernard & J. Weil, Rev. de la tuberc., 1946, 10: 157.*—(V. Leites)

Fever after Refills.—Fever up to 103° to 104° following pneumothorax refills was observed in certain cases with good collapse, controlled lesions and dry pleural space. Since no pleural or pulmonary origin of the fever can be invoked in these cases, the fever is probably due to a disturbance of the vegetative nervous system, with predominance of sympathetic stimulation. In 3 such cases the febrile reaction could be eliminated by two subcutaneous injections of yohimbine, (10 mg.), administered immediately after the refill and before the presumed onset of the fever.—*Fièvre nerveuse de réinsufflation, R. Even & J. Lecocur, Rev. de la tuberc., 1946, 10: 86.*—(V. Leites)

Empyema in Pneumothorax.—Among 450 pneumothorax cases under observation the incidence of empyema was 6.6 per cent. Two main groups were distinguished: (1) empyema cases without evidence of a bronchopleural fistula; (2) empyema with demonstrable bronchopleural fistula, the perforation being latent, intermittent or widely open. The first group of cases with "closed pleural space" is divided in three subgroups: (a) so-called pleural "cold abscess," characterized by empyema rich in tubercle bacilli, developing slowly and with a

minimum of clinical symptoms in cases with initially clear serous effusion; (b) tuberculous empyema with sudden onset, accompanied by high fever and marked constitutional symptoms; (c) tuberculous empyema complicated by mixed infection. An outline of the treatment of these various forms is given, illustrated by case histories.—*A propos de 50 cas de pleurésies purulentes du pneumothorax, valeur du drainage avec aspiration continue, M. Bertheau, Le Poumon, March-April, 1946, 2: 101.*—(V. Leites)

Complications of Pneumothorax.—The authors do not believe that the complications usually ascribed to prolonged pneumothorax treatment, such as thickening of the pleura, hemorrhagic pleurisy and empyema, are actually due to the pneumothorax itself, that is, to the presence of air in the pleural cavity and the prolonged traumatization of the pleura by refills. The incidence of pleural complications is not considered higher in old pneumothoraces than in cases of recent pneumothorax or after reëxpansion. A series of other conditions is described, which are considered real complications of prolonged pneumothorax treatment. One of them is anoxemia, occurring as a late complication of pneumothorax and manifesting itself by anorexia, progressive weight loss without apparent cause, and sometimes asthenia and fever. This condition is apt to develop in cases with excessive collapse or extensive lesions. Improvement can be achieved by partial reëxpansion. These patients should not be treated at high altitudes. Another disadvantage of pneumothorax is seen in its unfavorable effect on endobronchial lesions. In tuberculosis associated with bronchiectasis, pneumothorax may impair drainage and increase the degree of bronchial dilatation and retention. Bronchoscopic aspiration may give good results in these cases. If this is ineffectual the degree of collapse should be reduced or reëxpansion considered. Subsequent resection may be necessary. Another complication is observed in cases with narrowing of the large bronchi in which pneumothorax will increase the degree of stenosis.

To those who are apprehensive of the risks of prolonged pneumothorax treatment the authors retort that although continuation of pneumothorax is associated with certain dangers, the interruption of pneumothorax does not necessarily eliminate them. These dangers are: (1) Postpneumothorax empyema due to active pulmonary lesions. The lesions may never have been completely controlled by pneumothorax and reactivation sets in after reëxpansion or there may be formation of new lesions in the reëxpanded lung. If the diseased area is peripherally located there is great danger of perforation with formation of a partial pneumothorax and subsequent pyogenic infection. (2) Postpneumothorax empyema of pleural origin; in cases of so-called fibrothorax latent residual fluid collections are often present, recognized or unrecognized. Inter-current diseases or break-down of the general resistance may lead to the development of mixed infection in these fluid pockets. If early treatment is not instituted the breakthrough of the septic fluid into the bronchial tree has been observed repeatedly by the authors as late as ten to twenty years after reëxpansion.—*La pathologie tardive du pneumothorax artificiel, F. Dumarest & H. Mollard, Le Poumon, May-June, 1946, 2: 129.*—(V. Leites)

Open Pneumonolysis.—In 1925 Alexander, reviewing all reported cases, reported "that thoracoplasty is preferable to pneumothorax which must be preceded by so risky an operation as open intrapleural pneumonolysis." But he wrote again in 1937, "developments in the technic of open intrapleural pneumonolysis have made the operation a valuable one for a small group of patients." The author reports 15 cases of open pneumonolysis without contralateral spread or activation of disease, and success in every case. There was no morbidity, no wound infection, and no empyema. Brief transcripts of these cases are given. All adhesions are released in the endothoracic fascial plane. This prevents injury to the lung. All bleeding points are sutured with silk. The ribs are approximated with one

braided silk suture passed through the ribs and not around them. No attempt is made to close the pleura or intercostal space. Chest wall is closed with interrupted silk sutures throughout. The pneumothorax space is adjusted by air introduced by syringe and needle. On return to the ward patients are given 30,000 units of penicillin every three hours. Carbon dioxide inhalations are given every three hours and patient is turned frequently. Oxygen tent is used for first twenty-four hours. Bronchiolar spasm is relieved by adrenalin in oil. Air refills are given as necessary under fluoroscopic or radiographic control. Aspiration of intrapleural fluid is done when needed. Patients are usually discharged in ten to fourteen days. It is important that open pneumonolysis be avoided in that group of patients where complications are frequent. It is commonly agreed that pneumothorax should not be done at all in those with a large tension cavity; when either fibrotic or tuberculous stenosis exists; or when atelectasis occurs. Rigid indications for open pneumonolysis are used. Those adhesions not severed by closed method were studied with open pneumonolysis in mind. Adhesions may not be too extensive or numerous; area of adherence to chest wall or mediastinum should not exceed an area equal to operator's palm; and there must be no evidence of pleural exudate, tubercles or pleuritis. True pleural effusions contraindicate open operation but small transient effusions will not.—*Open Pneumonolysis, O. C. Brantigan, J. Thoracic Surg., October, 1946, 15: 341.*—(W. M. G. Jones)

Extrapleural Pneumothorax.—Extrapleural pneumothorax is not new in the treatment of pulmonary tuberculosis, but the method of management has been developed during the past five or six years and, following the work of Graf and Schmidt, it has come into widespread use. Indications for it have not been definitely set forth and vary with the men using it, but it has been offered to a group of patients not suitable for other procedures with the hope that it would either arrest their disease or improve their condition so that thora-

coplasty could be employed. It is believed that extrapleural pneumothorax is indicated where collapse therapy is desirable but satisfactory intrapleural pneumothorax is unattainable and thoracoplasty is contraindicated. Most are cases having bilateral disease or toxemia due to exudative destructive disease contraindicating thoracoplasty. Extrapleural pneumothorax can be made the most selective of all types of collapse. The patient should be fluoroscoped every five hours for thirty-six hours following the operation and refills given as often as necessary to maintain the space. For the remainder of the week daily fluoroscopy and refills suffice. The pressure is gradually increased to produce more collapse. The sero-hemorrhagic exudate which forms, partially filling the space, is aspirated on the fifth or sixth day. If the space is not dry at the end of three or four weeks a tuberculous or pyogenic infection should be suspected. The immediate complications include rupture into cavities or pulmonary tissues, necessitating immediate abandonment of the operation, hemorrhage, shock, subcutaneous emphysema, rupture of cavities near the periphery, wound infection, contralateral spread, loss of the space and atelectasis of the lower lobe. Forty-eight patients are reported in whom 51 lungs were collapsed. The operation was successful in 88.4 per cent; there were no complications in 64.4 per cent and there was conversion of sputum in 75 per cent. There were no deaths from the operation; the late fatality was 8.3 per cent.—*Extrapleural Pneumothorax in the Treatment of Pulmonary Tuberculosis, F. H. Alley, Radiology, May, 1946, 46: 470.*—(G. F. Mitchell)

Extrapleural Pneumothorax.—Extrapleural pneumothorax was performed in 54 cases during a period of six years. Intrapleural pneumothorax had been attempted previously in all but one case, and 12 had had phrenic nerve operations. Every patient had a cavity on the operated side and changes of varying extent on the other. In some, thoracoplasty was considered but not done because of the instability of the contralateral lesions. In the

others, there was absolute indication for extrapleural pneumothorax. The operation is less formidable than thoracoplasty. Cases are preferred in which the lesions do not extend below the fifth rib posteriorly. Otherwise, the size, character and position of the lesions is immaterial. If conditions change, a thoracoplasty can be done later. The following are special indications for extrapleural pneumothorax: (1) severe toxemia; (2) relatively recent infiltrative disease; (3) age of patient—ages below 14 (because of spinal deformity) and over 50 are contraindications for thoracoplasty; (4) for control of hemorrhage; (5) large cavities situated in centre of apex of lung which tend to flatten out against mediastinum in thoracoplasty; (6) active disease of opposite lung; and (7) low vital capacity. In two-thirds of the cases, the spaces became obliterated after four years. Many of these patients remained well. In the cases where the space persisted, all but one did well. In 11 cases there was tuberculous infection of the extrapleural space and in 4 cases there was non-tuberculous infection. There were 8 deaths (14.8 per cent); one was due directly to the operation, 4 to spread soon afterwards and 3 to spread at least four years afterwards.—*Extrapleural Pneumothorax in the Treatment of Pulmonary Tuberculosis*, H. Reid, *Thorax*, December, 1946, 1: 211.—(A. G. Cohen)

Extrapleural Pneumothorax.—A follow-up is given of the 13 survivors of 17 cases of extrapleural pneumothorax which were started between 1939 and 1941. Some had been treated by extrapleural pneumothorax alone, some by extrapleural pneumonolysis according to Sebestyen and some by both methods combined. Of the 13 survivors, 2 died of pulmonary or gastro-intestinal complications eighteen and twenty-six months after operation. Eight had a positive sputum, 3 had a negative sputum and in 2 no sputum could be obtained. In 6 cases the treatment had to be abandoned because of complete symphysis or other complications. In 5 cases the treatment was discontinued as the lesion for which it had been started was apparently cured. One is

still maintained and one other case died while under treatment. Contralateral lesions were observed in 4 cases. A phrenicectomy and pneumoperitoneum were done in one case and a phrenicectomy alone in another case. Despite apparent closure of the cavity and disappearance of expectoration, gastric contents contained acid-fast bacilli in many cases. The authors come to the conclusion that extrapleural pneumothorax has to be maintained for at least two years. If the cavity is not closed within six months this treatment, even if maintained for a long time, will not result in final closure and should be abandoned. In cases in which the extrapleural pneumothorax was discontinued because of apparent healing of the lesion, healing has persisted after a period of observation which varies from one and one-half to four years.—*Pneumothorax extrapleural, Evolucion de los casos comunicados en 1941*, R. F. Vaccarezza, O. A. Vaccarezza & J. Rey, *An. Cated. de pat. y clin. tuberc.*, June, 1945, 7: 125.—(W. Swienty)

Extrapleural Pneumothorax and Penicillin.—Two case reports of extrapleural pneumothorax complicated by staphylococcus infection. In the first case penicillin was administered locally through a tube (total amount 170,000 units), and intramuscularly in the second case (total amount 920,000 units). In both cases the treatment was considered as life saving. The infection was brought under control, and the extrapleural space could be maintained.—*Traitement de deux complications de pneumothorax extrapleurales et leur sauvetage par la pénicilline*, M. Averous, *Rev. de la tuberc.*, 1944-45, 9: 503.—(V. Leites)

Extrapleural Pneumonolysis.—A case of pulmonary tuberculosis is reported with a large cavity in the right upper lobe which failed to close after induction of pneumothorax and a two-stage intrapleural pneumonolysis. The lung was entirely adherent to the mediastinum. A two-stage extrapleural mediastinal pneumonolysis was performed liberating the lung from the apex to the diaphragm. During the second stage it became necessary to sever

the phrenic nerve. Six weeks later the cavity was not demonstrable on X-ray films and there was conversion of the sputum. The authors have performed 95 extrapleural pneumonolyses, 26 of these along the mediastinal surface. No serious complications were encountered.—*Désinsertion extrapleurale du médiastin en deux temps avec phrénicectomie de nécessité*, J. Braillon, *Rev. de la tuberc.*, 1946, 10: 52.—(V. Leites)

Instrument Tray for Chest Surgery.—A simple instrument tray is illustrated which fits the contour of the hip or the thigh of any patient in the latericumbent position which is in common use for many types of operations. The legs of the tray are pliable and adjust to any hip. It may be used under the sterile drape or on top of it. Illustrations are self-explanatory.—*An Accessory Instrument Tray*, Beatrice H. Aufses, *J. Thoracic Surg.*, August, 1946, 15: 298.—(W. M. G. Jones)

Support for Patients during Chest Operations.—The author gives detailed description with diagrams of a simple adjustable wooden support or trough in which the patient lies during thoracoplasty or similar operation. It can be made by any carpenter and should be welcomed by the thoracic surgeon who has experienced difficulty in keeping the patient's position firm on the operating table.—*A Thoracic Support*, W. Spickers, *J. Thoracic Surg.*, April, 1946, 15: 145.—(W. M. G. Jones)

Primary Thoracoplasty.—Thoracoplasty without previous attempt at artificial pneumothorax is advocated in cases with unilateral apical cavitation on the ground that it is more certain, complete and permanent, less prolonged and expensive, and less risk of premature discontinuance or mismanagement. The surgical procedure is simpler and safer if undertaken without preliminary pneumothorax, which, if not associated with pleural infection or contralateral spread may still involve dangerous delay while the air is being absorbed, and consequent extension of the lesion requiring more extensive collapse.—*A Plea*

for Preferential Thoracoplasty in Early Apical Cavitation in Pulmonary Tuberculosis, P. L. Deshmukh, (Bombay), *Antiseptic (Madras)*, March, 1946.—(E. Bogen)

Results of Thoracoplasty.—A statistical review of 210 thoracoplasties is given, performed in Passy, France, between 1943 and 1945. The results were evaluated after a time interval of six months to three years, and were classified as complete, favorable, insufficient and poor. Complete results (60 per cent of cases) are defined as having no evidence of cavitation on X-ray films (including tomography), and a repeatedly negative sputum. Favorable results (16.2 per cent of cases) had X-ray findings as above, but the sputum was not negative, possibly due to contralateral lesions. As favorable results were also classified cases having presented very extensive cavitation preoperatively, which had been reduced by thoracoplasty to a residual slit. Insufficient results were obtained in 11.4 per cent of cases, the cavity having failed to close. In 5 of these cases subsequent Monaldi drainage or cavernostomy brought the disease under control. Thus, the total of good results was 83 per cent; and 12.4 per cent of cases were classified as poor results (persistence of active lesions, spreads). This group also includes 18 deaths. Postoperative complications occurred in 32 cases, and was mainly due to postoperative flare-ups and spreads, rupture of the pleura during operation, pneumothorax pleurisy on the contralateral side and wound infection.—*Statistique de 210 thoracoplasties pratiquées en deux ans dans un centre sanatorial*, H. Joly & C. Carcopino, *Le Poumon*, July-August, 1946, 2: 237.—(V. Leites)

Complications of Thoracoplasty.—The incidence of fatal complications after thoracoplasty is estimated at about 3 per cent. The fundamental aspects are distinguished: (1) massive pneumonia of the lower lobe on the side of operation; (2) asphyxia due to pulmonary edema. These forms of postoperative pneumonia are considered similar in character to those described by Virchow as "hemorrhagic

pneumonia," *Spritzpneumonia* and found in the victims of Koch's tuberculin therapy. Thus, an important number of postoperative pneumonias are probably the result of autotuberculinization, caused by traumatized tissue. The starting points of these reactions are old fibrocaseous foci considered as arrested and often even invisible. Although no conclusive evidence is as yet available, the preoperative administration of anti-histamine substances (described as 2339F) is advised. Another group of postoperative pneumonias is caused by bronchogenic aspiration. The unfavorable action of phrenic nerve paralysis in patients undergoing thoracoplasty is not only attributed to the inhibition of expectoration and stagnation of secretions, but also to the elimination of the sympathetic fibers within the phrenic nerve (cholinergic, adrenergic, histaminergic). The inhibition of their action cannot be without important consequences on the vegetative control of lung tissue, which may be the most important factor in the development of lesions. But these points are admittedly hypothetical.—*A propos des complications des thoracoplasties: Comment on peut les prevenir, J. Rolland, Rev. de la tuberc., 1946, 10: 117.*—(V. Leites)

New Incision for Thoracoplasty.—The author points out that the usual scapula-mobilizing incision cuts through the thick muscle mass of trapezius and rhomboids, latissimus dorsi and part of the serratus magnus. This is objectionable from several standpoints: hemorrhage is often considerable; the posterior scapular artery on deep aspect of the rhomboids is often divided; part of the muscle has its nerve supply cut and becomes atrophied and fibrous; cut muscle is indifferent or poor material to suture, and rupture opens extrafascial spaces to the exterior; function of these cut muscles cannot be perfect, especially when subjected to repeated section. The modification suggested here has been used for a year and seems to avoid most of these disadvantages. The usual curved incision is made down to, but not through, the muscles of the back. The vertical part of the incision is

made two finger breadths from the mid-line. The medial flap is now undercut its whole length, exposing most of the trapezius to within 2 inches of its lowest origin. The latissimus dorsi is sectioned as usual, but the trapezius only across its lowest fibers. With a finger the rest of the trapezius muscle is now separated from the aponeurosis covering the erector spinae muscles, and with scissors or knife, it is cut as near as possible to the spinous processes. This division of the trapezius close to the mid-line is carried right up to the top of the wound. The rhomboid muscles are raised with the trapezius; the serratus posterior superior may be included, or left on the ribs, as desired. As this aponeurosis of the trapezius is being cut one should watch for and secure the medial divisions of the posterior branches of intercostal vessels and for the lateral divisions of the same as the flap is displaced forward. At the end of the operation the muscle layer is sewed back to its original attachment to the spinous process and its ligaments. This is easy to do and only one layer of sutures is needed, although a few interrupted reinforcing sutures may be added. Reopening of the wound in the same manner is equally easy and quite bloodless. By this method the disadvantages mentioned before are avoided; exposure is improved; the two suture lines are not superimposed; bleeding is less.—*A Musculoplastic Incision for Posterior Thoracoplasty, R. C. Brock, J. Thoracic Surg., June, 1946, 15: 182.*—(W. M. G. Jones)

Revision Thoracoplasty.—A study of 89 revision thoracoplasties was made to determine why these patients failed to have satisfactory collapse of the lung, what could be done to insure better thoracoplasty results and what should be done in cases which do not respond satisfactorily to the classical thoracoplasty. Of the 62 patients with unilateral caseous pneumonic tuberculosis, a revision thoracoplasty failed to have satisfactory results in 47 (75.8 per cent). In the group of cases in which classical paravertebral thoracoplasty should give about 90 per cent satisfactory results, those with cavities in the upper outer

division of the lung field, the revision operation was unsuccessful in about two-thirds of the cases. Other factors than cavity location are significant in thoracoplasty failure. Causes of failure in the original operation in the 62 unilateral cases were: pneumothorax still present, (10 cases); thickened parietal pleura, (9 cases); anterior position of cavity, (9 cases); marked fibrosis of lung, (7 cases); inadequate or inopportune surgery, (12 cases); giant or parahilar cavities, (9 cases). Revision operation was uniformly successful only in those cases in which long posterior rib stumps had been left intact at the first operation; in all other cases the percentage of successful revisions was 24.2. Results of revision thoracoplasty in 27 patients with bilateral disease were essentially similar: approximately two-thirds of the patients having cavities in the upper outer segment of the lung did not benefit by revision operation; complete failure obtained in 4 cases having pulmonary fibrosis and in another 4 with markedly thickened parietal pleura; inadequacy of the original operation provided 4 successes in 8 cases. Death occurred in 24 of the 89 patients: 27.4 per cent in the unilateral, 26.0 per cent in the bilateral group. Acute postoperative spread, shock and hemorrhage caused deaths immediately; extension of the disease, debility following additional surgical procedures, progression of uncontrolled disease and one suicide accounted for the later deaths. Because of the low percentage of successful revision thoracoplasties and the high mortality rate, other means of controlling the disease should be adapted whenever possible.—*The Revision Thoracoplasty: A Study of 89 Cases*, L. A. Hochberg, I. Fink & A. Deniz, *Quart. Bull. Sea View Hosp.*, July, 1946, 8: 205.—(P. Q. Edwards)

Partial Claviculectomy.—Most cases of chronic empyema can be treated successfully by the use of multiple surgical procedures: extrapleural thoracoplasty, Schede thoracoplasty, pedicled muscle graft implantation with or without partial scapulectomy. By these measures the posterior empyemal spaces are obliterated, but in certain cases the space

extends also anteriorly and laterally and is held open by the clavicle. Removal of the first rib and its underlying parietal pleura fails to effect collapse because the extrathoracic tissues are held out by the clavicle anteriorly. The clavicle tends to rotate posteriorly following removal of the first rib, and, in so doing, some elevation of the scapula occurs. However, the length of the bone prevents approximation of the shoulder girdle to the chest wall, and, if infection is present in the space between, healing will not take place. Similarly, in subscapular space infections following thoracoplasty either for pulmonary disease or for empyema, drainage may persist for a long period of time due to the failure of the subscapular space to obliterate. The author presents 3 cases, in all of whom the infected space has been markedly diminished in size. The procedure is simple. Following removal of the clavicle the shoulder girdle will rely for support upon the trapezius and rhomboid muscles. Should these not be intact, as in cases of posterior wound infection, there will not be sufficient support of the shoulder girdle to hold up the arms. Following removal of the clavicle there is an immediate descent of the shoulder and scapula with an approximation of the shoulder girdle to the chest wall. Motion in the arm is retained with full strength to the horizontal level of abduction. The clavicle regenerates at the site of its periosteal bed in an irregular form analogous to the appearance of regenerated rib. With the clavicle absent there is more deformity than there is when it is intact, the shoulder being appreciably lower and closer to the chest wall than it is on the normal side.—*Partial Claviculectomy as an Adjunct to Surgical Collapse of the Chest Wall*, A. Lambert, J. Thoracic Surg., August, 1946, 15: 266.—(W. M. G. Jones)

Oxidized Gauze in Thoracoplasties.—“Oxidized gauze” (soluble cellulose) is a valuable addition to the hemostatic armamentarium. It provides, in an easily handled form, a packing material which can be safely left in a wound with no fear of its remaining as an

irritating or permanent foreign substance. Its use in clean wounds does not delay healing, nor does it interfere with the strength of union of tissues. When soaked with blood it has no strength of fiber, but rapidly becomes a sticky mass which is admirably adapted to packing deep narrow cavities either in soft tissues or in relation to raw bony surfaces. Oxidized gauze was not used in infected wounds, nor on serous membranes. In wounds subjected to a powdering with sulfathiazole, its action is unhindered. The technique of thoracoplasty calls for formalinization of rib periosteum, but as the oxidized gauze is sterilized in formalin, no ill effect follows from use here. (Oxidized gauze is marketed by Parke, Davis & Co. under the trade name of "Oxycel," and by Johnson & Johnson under the name of "Hemo-Pak.")—*Report of a Clinical Trial of Oxidized Gauze in Seven Thoracoplasties, R. A. S. Cory, J. Thoracic Surg., August, 1946, 15: 261.*—(W. M. G. Jones)

Intracavitary Drainage.—This report covers the Edward Sanatorium experience for the years 1941-1944. "Intracavitary suction should never be used when any other form of treatment is applicable. It is indicated for quiescent cavities of relatively long standing which are not surrounded by 'soft' active disease in patients in whom low vital capacity precludes the use of other measures. It is also of value in reducing the size of extremely large excavations as a preliminary to thoracoplasty." To avoid the development of empyema the operation should be divided into two or three stages. At the first stage the pleura is explored through a small intercostal incision if the catheter is to be inserted from in front, or by resection of a small piece of rib, if the catheter is to be inserted from the back. If adhesions are found the wound is sutured, and the catheter inserted one or two weeks later. A small amount of lipiodol or a small metal clip is left at the level of the pleura for X-ray check on relation of site to the cavity. If a free pleura is encountered a small iodoform gauze pack with metal clip is left on the pleura for ten to fourteen days, at which time the

presence of adhesions is verified. The wound is again sutured and one week later the catheter is inserted. The placing of the catheter requires extreme care. The cavity is located first by exploratory aspiration with a long 19-gauge needle, which can be assumed to be in the cavity when air or pus can be freely aspirated. The depth of the cavity is then noted and marked on the cannula which is the type used in draining the gall bladder and will admit a No. 14 French catheter. Trocar and cannula are inserted to determined depth and catheter put in a little deeper than the mark. After the cannula is removed, the catheter is pulled out a trifle, leaving 1 inch within the cavity. It is extremely important that the tube be fixed firmly in place by an air tight adhesive dressing and that great care is taken to keep it in place. Continuous suction is maintained for six to ten months through a trap bottle and Stedman electric pump. Then for a month the open catheter is left in place. If the cavity reopens suction is again applied; if it remains closed, the tube is removed. Results: of 29 patients, 13 are dead, but at autopsy, 3 of these had closed cavity. Of 16 living patients, 13 have closed cavity and 7 negative sputum; only 2 are worse. Twenty-two of the 29 patients had too extensive disease and too little vital capacity to permit any other form of treatment; 11 of these 22 are well or greatly improved. In 7 early cases the procedure was used in patients who might have been treated otherwise; 2 of these are well.—*Intracavitary (Monaldi) Suction, J. R. Head, J. Thoracic Surg., June, 1946, 15: 153.*—(W. M. G. Jones)

Congenital Tuberculosis.—When an infant dies in the first few weeks of tuberculosis, incompatible with postnatal infection because of extent, the diagnosis of congenital tuberculosis is warranted. In such cases, a primary lesion is found in the liver, with extensive involvement of the lymph nodes at the hepatic hilum. In rare cases, this primary complex is absent. Instead, extensive pulmonary changes are found. These

differ from the usual changes of postnatal tuberculosis in that no distinct primary focus is found. The lungs are peppered by small submiliary deposits. The hilar nodes are involved in a diffuse manner without topographical gradation. Seven such cases were reported up to 1939. The authors report the case of an infant who died on the seventeenth day of life. The mother was perfectly well. The deposits in the lungs were found to be bronchogenic in nature. The extensive cellular reaction about the lesions indicated an age greater than seventeen days. These lesions resembled those found in experimental animals infected intratracheally by tubercle bacilli. The conclusion is that this was a case of prenatal tuberculosis resulting from aspiration of infected amniotic fluid.—*Aspiration Type of Congenital Tuberculosis*, W. Pagel & S. Hall, *Tubercle*, October, 1946, 27: 153.—(A. G. Cohen)

Inoculation Tuberculosis.—A 25-year-old white Army officer received multiple superficial wounds of the face, in part from shell fragments and in part from splinters of wood. The fragments were excised and the wound healed without complication. About a month later a tender swelling appeared just lateral to the external canthus of the right eye, at a point where a fragment of wood had been excised. At the same time a tender swelling was noted below the right mandible. Under treatment with hot compresses, the facial lesion broke down and formed an ulcer. The ulcer and the lymph node were excised, since they suggested a malignant lesion. The histological diagnosis was tuberculosis, acid-fast bacilli were demonstrated in both lesions. A tuberculin test was positive. The patient received X-ray and ultraviolet therapy. At a follow-up examination four months later the scars were well healed. In the area of the ulcer, however, there were two small lesions interpreted as active tuberculous lesions.—*Inoculation Tuberculosis*, H. E. Bass, J. A. M. A., November 30, 1946, 132: 785.—(H. Abeles)

Tuberculosis of Skin.—The primary tuberculous complex of the skin consists of a series

of clinical events following the introduction (and multiplication) of tubercle bacilli into the skin. A small indolent inflammatory nodule or ulcer appears from one to three weeks after inoculation. Four to ten weeks later regional adenitis, with or without lymphangitis, follows. The adenitis is the most striking feature of the disease. As a rule the disease is comparatively benign and the process may heal within a few months. Less frequently the enlarged nodes undergo caseation necrosis and the process may extend to other groups of lymph nodes. Draining sinuses result. Generalized tuberculous infection including pulmonary disease sometimes follows. Theoretically a diagnosis of primary tuberculous complex of the skin is not acceptable unless it can be demonstrated that the patient did not have tuberculosis previous to the onset of his clinical lesions. Reinoculation tuberculosis of the skin may so closely simulate the primary skin complex as to be indistinguishable from it. It may be impossible to establish the diagnosis in adults, particularly in those of advanced age. The author reports the case of a 64-year-old woman who presented the clinical picture of the primary tuberculosis complex of the skin. She became inoculated with virulent tubercle bacilli when kissed by her husband who was dying of tuberculosis. The rapid appearance of the tuberculous lesion on the lower lip, followed within five or six weeks by cervical adenitis, and the subsequent involvement of other nodes on both sides of the neck with caseation fulfill the criteria for the primary tuberculous complex of the skin. The clinical course of the disease appeared benign until one year before death. Other chains of lymph nodes later became involved, and finally symptoms of pulmonary tuberculosis appeared. Inoculation of a guinea pig and bacteriological and histological studies of the affected tissues confirmed the tuberculous nature of the infection. Postmortem examination failed to show grossly the presence of healed tuberculosis. Nevertheless the case must be regarded as one of reinfection tuberculosis.—*Primary Tuberculous Complex of the Skin: Occurrence in a Woman Aged*

Sixty-four, N. N. Epstein, Arch. Dermat. & Syph., May, 1945, 51: 317.—(J. S. Woolley)

Classification of Tuberculosis of Skin.—Present day classifications tend to stress one or another of the following points: (1) mode of arrival of the bacillus at the site of the cutaneous lesion; (2) clinical features; (3) histological and bacteriological features; (4) immunological status; and (5) prognosis. The clinical features of the various forms of cutaneous tuberculosis afford the most important information, since it is impossible even to begin a classification unless the various tuberculodermata can be correctly recognized and given specific names. Even clinically one form of skin tuberculosis is sometimes indistinguishable from another yet, all in all, the clinical features of tuberculodermata are consistent, and from a practical standpoint this is important. Tuberculosis of the skin may be divided into two main groups: (1) the stable forms, as exemplified by *lupus vulgaris*; and (2) the labile, or transient forms, typified by the tuberculids. Bacteriological observations, except for rare types of cutaneous tuberculosis, are not a great help in forming a classification. Bacilli may be easily found only in primary cutaneous tuberculosis, the ulcerating orificial type and generalized miliary tuberculosis of the skin. Ascertaining the degree of allergy (tuberculin skin test) is essential in completing the study of a patient with tuberculosis of the skin. It must be borne in mind that an internal focus may be responsible for a positive test and not necessarily the cutaneous lesion. The most acceptable classification of tuberculosis of the skin is the one which enables the physician to make a prognosis. On this basis certain tuberculodermata may be grouped together, and if those in the same group are critically analyzed, common characteristics can be found which assist in classification. With this in mind the following classification of cutaneous tuberculosis is suggested:

A. Forms which are chronic and progressive, rarely terminating fatally

I. *Tuberculosis cutis luposa*
II. Tuberculosis in the American Negro (cause debatable)

III. Sarcoidosis (cause debatable)

B. Forms which tend to heal

I. Relatively rapidly

a. Primary cutaneous tuberculous complex

b. *Tuberculosis cutis verrucosa*

c. *Tuberculosis cutis lichenoides* (lichenoid papular tuberculid)

d. *Tuberculosis cutis papulonecrotica* (necrotic papular tuberculid)

II. More slowly

a. *Tuberculosis colliquativa* (scrofuloderma)

b. *Erythema induratum* (necrotic nodular tuberculid)

c. *Tuberculosis miliaris disseminata faciei* (lupoid papular tuberculid)

C. Forms which usually terminate fatally

I. *Tuberculosis cutis miliaris acuta generalisata*

II. *Tuberculosis cutis orificialis*

In tuberculosis of the skin, even though various appropriate names are evolved, it must be understood that there is a close similarity and relationship between types. A diagram is given which shows two basic forms: the stable or long lived, as exemplified by *lupus vulgaris*, and the labile, or shorter lived, as exemplified by the tuberculids, with their various merging ramifications.—*Classification of Tuberculosis of the Skin*, H. E. Michelson & C. W. Laymon, Arch. Dermat. & Syph., August, 1945, 52: 108.—(J. S. Woolley)

Primary Tuberculosis of Conjunctiva.—

Primary tuberculosis of the conjunctiva is rare. Diagnosis is based on: (1) there is no other demonstrable tuberculous lesion elsewhere in the body; (2) the process is unilateral; and (3) there is involvement of the satellite, preauricular nodes and other regional nodes. In general, methods of inoculation on the conjunctiva are: (1) primary infection is exogenous by definition; (2) secondary infection may be exogenous (as by a finger touching the eye) or endogenous

(by the blood stream) or by direct extension (as in a lupus or from tuberculosis of the orbit). Five types of tuberculous lesions of the conjunctiva are listed: ulcerative, nodular, hypertrophic papillary, polypoid, tuberculoma. A case of primary tuberculosis of the conjunctiva of the ulcerative type is presented, which occurred in a 10-year-old white boy with no history of exposure to tuberculosis. He developed a small lump in front of the right ear and, two days later, another lump beneath the right angle of the jaw and, again two days later, a swelling in the right eye. Biopsy of the ulcer revealed granulation tissue containing typical tubercles with Langhans' giant cells. Special stains and cultures from the scrapings of the lesion revealed acid-fast bacilli. Roentgenological examinations of the chest and abdominal regions showed no abnormality. The Mantoux test (1:10,000 dilution of OT) was strongly positive.—*Primary Tuberculosis of the Conjunctiva*, A. A. Goldfarb & I. Seltzer, *Am. J. Dis. Child.*, August, 1946, 72: 211.—(O. Pinner)

Tuberculomata of Liver.—The author describes a case of multiple tuberculomata (massive tuberculosis) of the liver in a man of 42, terminating with miliary tuberculosis. No primary tuberculous complex could be demonstrated but a calcified lymph node was found in the ileocecal region. It is possible that this old focus became active and that bacilli escaped into the portal vein and peribacilli spread to the liver portal lymphatics and so spread to the liver and spleen. Caseous nodes in the porta hepatis and along the splenic vessels support this view.—*A Case of Multiple Tuberculomata of the Liver*, N. Ashton, *J. Path. & Bact.*, January, 1946, 58: 95.—(H. J. Henderson)

Tuberculosis of Tonsils.—Primary tuberculosis of the tonsils with a lymphatic component in the cervical nodes, usually just at the angle of the jaw, seems a fairly common occurrence. If the lesion in the tonsil is to be accepted as primary, it is essential that the patient have no pulmonary foci and show no

evidence of calcification in the hilar nodes. Statistics show that when these criteria are applied, 48 out of a series of 98 children in whom tonsillectomy was performed, showed histological evidence of tuberculosis of the tonsils. Similar figures were obtained by other investigators. The rational treatment of tuberculous cervical lymphadenitis should always include tonsillectomy.—*Zur Frage der primären Mandeltuberkulose und zur Behandlung der Halsdrüsentuberkulose*, E. Schlittler, *Schweiz. med. Wchnschr.*, November 30, 1946, 76: 1235.—(H. Marcus)

Lymph Node Tuberculosis.—Tuberculosis of the external lymph nodes is not a primary disease in the sense of an initial lesion. The disease should be treated locally and generally. The authors distinguish six different stages of lymph node tuberculosis: (1) benign lymphogranuloma; (2) caseo-purulent lymphoma; (3) lympho-fibro-granuloma; (4) fibro-lymphoma; (5) caseo-purulent lympho-fibro-granuloma; (6) calcified adenitis. Spontaneous healing may occur in any stage. Sanatorium care for children is important but there is no specific medication. Chemotherapy has not shown any advantages. Climate has no special influence. Heliotherapy acts by its bactericidal effect. The most important medical treatment is X-ray therapy. Its effect seems to be due to the destruction of the lymphocytes and resulting sclerosis of the lymph node tissue. Cold abscesses should be opened and treated with sulfanilamide. Total extirpation of a single caseous node is a good method but it should not be done in the beginning of the process, as there is risk of lymphatic and hematogenous spread. Under no circumstances should multiple masses be extirpated. Electrocogulation under local anesthesia may be employed.—*Tratamiento de la tuberculosis ganglionar externa*, O. A. Vaccarezza, *An. Cated. de pat. y clin. tuberc.*, June, 1945, 7: 157.—(W. Swienty)

Bone Tuberculosis.—Systematic X-ray studies of the entire skeleton in 42 children

with primary tuberculosis revealed tuberculous foci in 40.5 per cent of cases. The X-ray changes which were considered as a basis for the diagnosis of tuberculous bone involvement were as follows: (1) Swelling of the soft tissues surrounding the diseased joint; (2) osteoporosis of the bones of the involved extremity; (3) more or less clearly outlined foci of bone rarefaction. Isolated foci showed in their earlier stages unsharp demarcation; they were roundish or oval, they were up to 0.5 cm. in diameter. In later stages these foci were clearly delineated, larger in size (up to 1.5 cm.). They were mostly located in the metaphysis or epiphysis of the long bones. The highest incidence was found in children with protracted primary tuberculosis. It is emphasized that definite osseous foci as demonstrated by X-ray films were clinically absolutely silent and often remained so during the further course. Most often a single bone focus was found. The majority of lesions was found in the proximity of the knee-joint, that is, in the lower epiphysis and metaphysis of the femur and the corresponding regions of the tibia. After routine discovery of such osseous foci close follow-up is recommended.—*Isolated Tuberculous Osseous Foci during the Phase of the Primary Complex in the Lung*, J. P. Parfenova, *Probl. tuberk.*, 1946, No. 1, 33.—(V. Leites)

Tuberculous Arthritis.—Taken singly, the roentgen signs of tuberculous arthritis are not pathognomonic. But taken together and in sequence they are sufficiently reliable for an accurate diagnosis. Tuberculosis of a joint is a metastatic process and may be in the synovial membrane or the bone contiguous to it. Early diagnosis is usually precluded by the insidious onset and X-ray diagnosis lags behind clinical diagnosis. The life history of an active tuberculous arthritis is as follows; cortical erosion, osteoporosis, loss of joint space, invasion of underlying cancellous bone, involvement of the opposing surface of the joint, absence of reactive changes, formation of sequestra, accumulation of debris,

rupture of the joint capsule with tracking of the fluid and debris resulting in cold abscesses and luxation of the joint. Some of these signs appear concurrently and increase in intensity with the increasing severity of the joint disease. No part of the joint is immune to a tuberculous infection and, if unchecked, will ravage every portion of it.—*Tuberculous Arthritis of the Shoulder*, M. R. Camiel, *Radiology*, June, 1946, 46: 569.—(G. F. Mitchell)

Surgery in Bone Tuberculosis.—Surgical interventions in osteo-articular tuberculosis are divided in (1) auxiliary, (2) radical, (3) correcting procedures. Auxiliary operations intend to create the most favorable conditions for the healing of the tuberculous lesion through operative fixation, without attacking the lesion itself (spinal fusion, arthrodesis). Radical operations, having the purpose of removing the tuberculous focus from the organism were employed predominantly in tuberculosis of the knee joint. The so-called "economical" resection was performed as a final act of conservative treatment. In addition to resection after opening the joint, a special technique of extraarticular resection is described. The correcting interventions, consisting mainly in osteotomy, are performed for improvement of abnormal positions which have developed as a result of the arrested tuberculous process. The liberal use of blood transfusions highly improved the results of the mentioned interventions reducing the postoperative mortality. One thousand nine hundred operations, performed over a period of twenty-five years, are reviewed. Surgical procedures were used in about 40 per cent of cases with osteo-articular tuberculosis. Radical operations of the prophylactic type of bone resection were performed only in 10 per cent of cases. Half of these were resections of periarticular osseous foci, the other half were in the diaphysis and especially in the calcaneus. Resections of the "economical" type were performed in 40 per cent of cases. The majority of these concerned the knee-joint. One hundred

fifty spinal fusions and 50 intraarticular arthrodeses of the hip joint were performed. In tuberculosis of the spine the immediate operative results were favorable in 88.8 per cent of cases, as compared with 64.7 per cent if conservative treatment alone was employed. The outcome was unfavorable in 2.9 per cent and 7.6 per cent died. In tuberculosis of the hip joint the immediate favorable results were 91.6 per cent as compared with 67 per cent with conservative treatment; 3.1 per cent were unfavorably influenced and 4.6 per cent died. The mortality was 10.8 per cent with conservative treatment. In tuberculosis of the knee joint surgical treatment produced 98 per cent favorable results, conservative treatment 72 per cent. The mortality was 1.1 per cent with surgery, 6.7 per cent with conservative treatment. The remote favorable results in tuberculosis of the spine, the hip joint and of the knee were 74.5 per cent, 85 per cent and 95 per cent, respectively.—*Remote Results of Surgery in Osteo-articular Tuberculosis*, P. G. Korncv, *Probl. tuberk.*, 1945, No. 5, 15.—(V. Leites)

Tuberculosis of Uterus.—Two forms of tuberculosis of the uterus are recognized, caseous exudative endometritis and disseminated productive disease which involves the endometrium and the muscular layers. When seen at an early state, the two forms can be well differentiated. Caseous endometritis is somewhat more common and always originates by extension of a tuberculous caseous process from the Fallopian tube. It is often combined with tuberculous peritonitis and also with other evidence of protracted dissemination. The prognosis is usually poor, in so far as the function of the generative tract is concerned. Disseminated uterine tuberculosis shows small productive foci in the myometrium and in the endometrium. There is little tendency to caseation and local spread, with rupture of a focus into the uterine cavity. Such foci may remain indolent and unchanged for years. They are usually not discovered, unless specimens obtained from curettage are ex-

amined systematically for this condition. Often only histological examination at autopsy gives evidence of this form of uterine tuberculosis. When the diagnosis is made by scraping, it is important to differentiate the two conditions because of the difference in prognosis. Primary exogenous infection of the genitalia has been claimed, but no convincing case has been published. There is no tendency for a local tuberculous lesion of the perineum to ascend and thus produce tuberculosis of the uterus and tubes.—*Die Pathogenese der Uterustuberkulose*, W. Berblinger, *Schweiz. med. Wchnschr.*, November 30, 1946, 76: 1223.—(H. Marcus)

Genito-urinary Tuberculosis.—At Fitzsimons General Hospital, the ratio of admissions for pulmonary to genito-urinary tuberculosis was 33 to 1. There was a high incidence among Negro and American Indian troops. There was no previous history of tuberculosis. Cases of tuberculosis of the kidneys or epididymis comprised almost the entire series. Only 20 per cent of the cases showed active or inactive pulmonary tuberculosis. There was a greater incidence of pulmonary tuberculosis with renal than with epididymis involvement. Other forms of extrapulmonary tuberculosis were not common; of these, involvement of the bones and joints was most frequent. Most of the renal cases were early. They were usually detected in the course of evaluation of pyuria. The most frequent symptoms were mild discomfort in the back and fever. A few patients had bladder symptoms. In many, pyelography was inconclusive. Retrograde pyelograms usually yielded better information than the intravenous. Great reliance was placed upon cultures of the urine for tubercle bacilli. Cultures were more accurate than smears. Guinea pig inoculations were not done. Bilateral cases were rare. Nephrectomy was the treatment of choice unless cultures showed involvement of the other kidney. However, if the involved kidney was badly diseased while the other kidney was only slightly involved, then nephrectomy was

done anyway. Operation was not done if there was pulmonary tuberculosis unless this was quiescent. There were no operative deaths. In tuberculous epididymitis, the lesion was bilateral in 28 per cent. Renal tuberculosis was present in 30 per cent and pulmonary tuberculosis in 13 per cent of the cases. The first symptom was painful swelling in the scrotum. This was gradual in onset. The whole epididymis was greatly enlarged, hard, nodular and irregular, but not extremely tender. It was often adherent to the scrotum with or without sinus formation. In a few cases, the testis was involved. The vas deferens was involved in most, and also frequently the prostate and homolateral seminal vesicle. Epididymectomy was the treatment of choice.—*Tuberculosis of the Genitourinary Tract among Soldiers in World War II*, R. Chute, *New England J. Med.*, October 17, 1946, 235: 586.—(A. G. Cohen)

Genito-urinary Tuberculosis.—Tuberculosis of the kidney, both in the male and in the female, is undoubtedly due to hematogenous dissemination of the disease. No convincing case of ascending renal tuberculosis from genital tuberculosis in the male has been reported to date. In the male, the majority of cases of genital tuberculosis originate in the prostate. The spread to the prostate occurs by way of the blood-stream. The seminal vesicles are also infected by the blood-stream, but tuberculosis of the ductus deferens and the epididymis occurs by intracanalicular spread. In a small proportion of cases the prostate appears to become infected by infected urine from tuberculous kidneys. This is undoubtedly an infrequent occurrence. In 35 carefully studied cases the possibility of this form of pathogenesis was considered in 5. In the female, tuberculosis of the tubes is apparently more often caused by extension from a tuberculous process in the peritoneum. Spread of the process throughout the tubes and the uterus occurs by direct extension. Hematogenous tuberculosis of the tubes and the uterus probably occurs too, but it is rare. In such cases the wall of the tube may contain

a tuberculous focus which eventually breaks into the tubal lumen. It is more usual that one is able to demonstrate extensive caseous changes in the mucous membrane lining the tube without definite changes in the muscular coat. In 35 cases, peritoneal tuberculous foci could be demonstrated 27 times in the vicinity of the tubal opening. Aside from the 70 cases mentioned above, the material for this study included two series of post-mortem material. Among 933 autopsies of pulmonary tuberculosis, 102 cases of genito-urinary tuberculosis were found, in another series of 445 cases, renal tuberculosis was found 82 times, or in 18.4 per cent.—*Die Urogenitaltuberkulose*, W. Berblinger, *Schweiz. med. Wchnschr.*, November 16, 1946, 76: 1171.—(H. Marcus)

Tuberculous Abscess following Penicillin.—The patient received a continuous intramuscular drip of penicillin in the thigh for about twenty-four hours. Four months later, he developed a fluctuant swelling at the site of the infusion. Upon incision, pus was found which, on study, revealed tubercle bacilli. Thorough investigation of the patient revealed no tuberculous foci in the lungs, spine or elsewhere. It is thought that tubercle bacilli were probably introduced through the infusion needle.—*Tuberculous Abscess following Intramuscular Penicillin*, D. Ebrill & S. D. Elck, *Lancet*, September 11, 1946, 2: 578.—(A. G. Cohen)

Changing Virulence.—The Gué strain of bovine bacilli, having been maintained on bile-potato media for several years, has partially lost its virulence. Two experiments were carried out with this strain to demonstrate altered virulence in successive guinea pig passages. In the first of this series, guinea pig A was inoculated with 0.1 mg. of bacilli of very attenuated virulence from a bile culture of 125 passages. From this animal a biopsied inguinal lymph node was implanted into pig B. Following four similar successive passages from pig to pig, the bacilli had not shown any return to virulence

in spite of their very long survival. On the other hand, following the death of pig A a caseous lumbar lymph node was inoculated into two successive guinea pigs, following the second such passage the bacilli developed a rapid return to normal virulence. The second experiment consisted of inoculating guinea pig C with 1.0 mg. of strain Gué after 134 bile passages. The pig died slowly of extensive tuberculous lesions. During the third month of its illness an inguinal lymph node was biopsied and inoculated into pig D. This node proved to be totally innocuous although a marked tuberculin allergy developed in pig D. When pig D died, of other causes than tuberculosis, one year after inoculation, the organs showed no trace of tuberculous lesions, but cultures from the macerated organs produced bacilli more virulent for guinea pigs than the original 134th passage Gué culture. There are two possible explanations for this alteration in virulence after successive animal passages: (1) possible dissociation of the virulent elements in the course of the disease. Nodes biopsied early in the disease prove to be less virulent than nodes removed at the time of the death of the animal. (2) There may be a gradual liberation of the already attenuated bacilli from the transplanted node, so that the host develops some immunity.—*Variabilité de la virulence d'une souche de bacilles tuberculeux bilités au cours de l'infection chez le cobaye*, F. van Deinse, *Ann. Inst. Pasteur*, July–August, 1946, 72: 567.—(P. Q. Edwards)

Respiration of Tubercle Bacilli.—Respiratory metabolism of several types of paratubercle bacilli was studied in an attempt to determine if group specificity could be established. Bacilli employed in the studies were: strain D6 from the intestine of an infant, B1 from a mesenteric node of an ox, Pellegrini's bacillus and *Bacillus C* from spinal fluid of a child. The respiratory activity of a given culture was found to be a function not only of the age of the bacilli but also of the alteration of the medium occasioned by bacillary mortality. All growth

phases of a culture of bacilli, including the phase when no death takes place, are accompanied by a more and more pronounced lowering of the respiration varying directly with the unit of bacilli present as well as the inevitable alteration of the milieu. Thus a means of determining the death rate of a given culture is established through measurement of its respiratory retardation. The paratubercle bacilli studied have certain physiological properties in common, including similarities in their respiration.—*Contribution à l'étude du métabolisme des bacilles paratuberculeux: II. Métabolisme respiratoire de divers types des bacilles paratuberculeux*, A. Andrejew, *Ann. Inst. Pasteur*, July–August, 1946, 72: 611.—(P. Q. Edwards)

Metabolism of Tubercle Bacilli.—Experiments concerning the respiration and growth of tubercle bacilli demonstrated that these two functions are largely independent. Certain substances augment the respiration of tubercle bacilli and at the same time increase their growth and multiplication; certain substances increase the respiration without affecting growth; other substances, while increasing the respiratory processes, depress or abolish multiplication. A substance of the latter order is sodium salicylate. Five different groups of substances are evaluated with respect to their capacity for affecting the respiration and growth of tubercle bacilli. The substances tested were primary amines and their derivatives, heavy metal compounds, sulfonamides, disinfectants and fatty acids. Results show that three different effects on tubercle bacilli were obtained. Heavy metal compounds, disinfectants and fatty acids produced their effects by irreversible damage to the bacterial cell. The respiration of the cell body was also severely damaged by these substances. The sulfonamides produced bacteriostasis of a nonspecific and reversible nature. In the presence of suitable antagonistic substances (p-aminobenzoic acid) the effect could be completely annulled. The effect of the sulfonamides on tubercle bacilli is no different from that produced on other

microorganisms. Cell respiration and the ability of the single cell to grow remains unimpaired, but division of cells, mitosis and multiplication are stopped. Of special importance is the action of the primary amines. These produced specific reversible effects on the multiplication of tubercle bacilli, without affecting respiration and growth. These substances had no effect on other microorganisms, but their effectiveness was from six to eighty times that of a 0.0002 molar solution of sodium salicylate.—*Über den Stoffwechsel von Tuberkelbazillen*, H. Bloch, *Schweiz. med. Wchnschr.*, November 16, 1946, 76: 1179.—(H. Marcus)

Fatty Acids and Bacterial Growth.—Unsaturated fatty acids retard the growth of tubercle bacilli, but these acids can be detoxified by their esterification or by the addition of native serum albumin to the medium. Enhancement of growth of tubercle bacilli can be obtained by adding 0.01 per cent of any of a variety of long chain fatty acids—saturated or unsaturated—to a medium containing 0.5 per cent crystalline serum albumin. Glucose is not necessary. The growth of *Micrococcus C* is increased in proportion to the amount of unsaturated fatty acids in the medium, and glucose further increases it. The saturated fatty acids do not support growth of *Micrococcus C*, and crystalline albumin inhibits the growth. At equal concentrations of long chain fatty acids, the water soluble esters are more efficient than the corresponding soaps in supporting bacterial growth.—*Effect of Long Chain Fatty Acids in Bacterial Growth*, R. J. Dubos, *Proc. Soc. Exper. Biol. & Med.*, October, 1946, 63: 56.—(F. B. Scibert)

Fatty Material in Bacteria and Fungi.—An improved technique for demonstrating intracellular lipid in microorganisms by staining dried, fixed preparations with Sudan black B, and counterstains is described. The application of this staining method to films of the principal species cultivated on common media revealed that stainable fatty material in the

form of cytoplasmic inclusions, or such material associated with structural elements of the cells, is present in all fungi and in the great majority of bacteria, whether these are aerobic or anaerobic, saprophytic or parasitic, pathogenic or nonpathogenic. Of greatest interest was the unexpected finding that the relative amount of stainable fatty material and its form and location within the cells of bacteria are remarkably constant for any one kind of organism. Definite differences occur among different kinds. Thus, the pattern of intracellular lipid exhibited in the stained films is to a considerable degree characteristic for the bacteria of a particular genus, and in some cases for those of a particular species.—*Fatty Material in Bacteria and Fungi Revealed by Staining Dried, Fixed Slide Preparations*, K. L. Burdon, *J. Bact.*, December, 1946, 52: 665.—(F. G. Petrik)

Disparity between Hansen's Bacilli and Cultured "Leprosy Bacilli."—By application of the writer's improved fat-staining procedure (Sudan black B) for dried preparations it was found that the principal varieties of acid-fast bacilli in culture show an essentially similar picture with respect to their stainable intracellular lipid. Characteristic of the whole group is the tendency of the cells to stain throughout with Sudan black B; in addition, distinct deeply colored fat droplets may be present within many of the rods. Some differences were noted in the amount of fatty material usually present, and in the regularity with which it occurred, in different varieties of these organisms. The constancy and prominence with which stainable lipid occurs in cultured "leprosy bacilli" was repeatedly confirmed, and their marked similarity in this respect to the tubercle bacilli of the "cold-blooded type," and to the frankly saprophytic acid-fast organisms, was made clear by numerous comparative tests. A modified stain was applied to direct films from leprosy lesions and the results were entirely consistent, that is, no intracellular stainable fatty material was observed in any

of Hansen's bacilli. The apparent total lack of stainable lipid in the true causative bacilli of leprosy is, at least, in striking contrast to the abundance of this material in the acid-fast bacilli isolated from leprosy lesions and now maintained in laboratory cultures. The full significance of this disparity is debatable, but it would seem justifiable to count it as adding a further bit of evidence in support of the already widely held opinion that the organisms in these cultures are not identical with the true causative agent of leprosy.—*Disparity in Appearance of True Hansen's Bacilli and Cultured "Leprosy Bacilli" when Stained for Fat*, K. L. Burdon, J. Bact., December, 1946, 52: 679.—(F. G. Petrik)

Bovine Type Bacilli.—A culture of tubercle bacilli originating from a case of pulmonary tuberculosis in man was obtained in 1933 by injecting acetone extract of bacilli into guinea pigs. Shortly after its isolation this culture appeared to be avirulent for the rabbit and normally virulent for the guinea pig. After having been maintained for more than a year on potato medium, this culture acquired a very marked virulence for the rabbit. Six years after its isolation the virulence for the rabbit began to diminish. The virulence for the guinea pig started to decrease during the eighth year after isolation. The culture was considered to be of the human type, but endowed with an exceptional pathogenicity for the rabbit. The colonies were eugonic and of the R type. Simultaneously with the above experiments the culture was grown on bile-potato medium since 1934, which produced a more marked and a more rapid decrease in its virulence than on simple potato medium. After the 125th transfer, serial passages were made from guinea pig to guinea pig. The culture regained a marked virulence for the rabbit and the guinea pig. It appeared now as a S type; its growth was dysgonic and it exhibited all the characteristics of a bovine culture. The conclusion is drawn that the original strain was actually of the bovine type.—*Une souche de bacilles tuberculeux de type bovin*

difficile a classer, F. van Deinsc, Ann. Inst. Pasteur, March-April, 1946, 72: 241.—(V. Leites)

False Acid-fast Bacilli.—Sudden increase in the number of acid-fast bacilli on smears from the chest wound (operative) of a tuberculous patient raised the question of false acid-fastness, in so far as the wound had been treated with sulfathiazole ointment prior to the noteworthy increase in bacilli. Several days after discontinuance of the ointment, the acid-fast bacilli present on smears decreased appreciably. Experimental *in vitro* reduplication of the phenomenon proved that diphtheroids, as well as *B. megatherium* and *B. coli*, are capable of being so coated with hydrous lanolin or petrolatum that they become acid-fast. This artefact may be eliminated by soaking fixed unstained smears successively in chloroform, ether and alcohol.—*False Acid-fast Bacilli*, A. Berczeller & Grace Frank, Quart. Bull. Sea View Hosp., July, 1946, 8: 187.—(P. Q. Edwards)

Dissociation of Tubercle Bacilli.—A guinea pig was inoculated through the mediastinal route with 2 mg. of a virulent bovine culture, presenting dysgonic growth on Löwenstein's medium. The animal died ten days later. Twelve cc. of a cloudy hemorrhagic fluid was found in the pleural cavities. Inoculation of this fluid on Laporte medium (egg-serum) produced smooth confluent colonies. One-half of the pleural fluid was diluted with citrate solution, the other half was permitted to coagulate. Both specimens were incubated at 38°C. Serial cultures made from these specimens remained negative until the thirty-fifth day at which time large conglomerations of typical acid-fast bacilli were found. On the forty-sixth day real colonies were visible macroscopically in the citrate specimen. In the eighth month after incubation 1.0 cc. of the citrate specimen was injected into a guinea pig which died of tuberculosis four months later. After a stay of one year in the incubator the coagulum became useless because of desiccation. At this time the

bacilli in the citrate specimen were found in a state of lysis. Their inoculation in the guinea pig produced generalized tuberculosis of a chronic type and predominantly lymphatic involvement. Death occurred seven months later. Inoculation of the organs of the animal on Löwenstein's medium gave rise to eugonic colonies of the R type, whereas the original bovine strain had been of the S type and dysgonic. The colonies were of normal virulence for the guinea pig and of diminished virulence for the rabbit. Inoculation of the same one-year-old fluid on Laporte medium and Besredka medium produced smooth dysgonic colonies. This culture appeared to be avirulent for guinea pigs and rabbits. Thus three different dissociates could be isolated in these experiments.—*Dissociation d'une souche de bacilles tuberculeux virulents de type bovin dysgonique en une variante avirulente également dysgonique et une variante virulente eugonique après séjour prolongé dans un liquide pleural de cobaye*, P. van Deinse, *Ann. Inst. Pasteur*, May-June, 1946, 72: 424.—(V. Leites)

Surface-Active Substances and Tubercle Bacilli.—The authors reported on the influence of fourteen surface-active compounds giving surface tensions in the range 50-24 dynes/cm. in a synthetic liquid medium upon the growth of three strains of acid-fast bacteria. The growth of *Mycobacterium tuberculosis*, human type, and *Mycobacterium phlei* was inhibited only at surface tensions below about 30 dynes/cm. The chemical nature of the depressant used did not appear to be a relevant factor. The medium containing depressants showed an increase in surface tension during growth, tending to the value of the unheated medium, showing that these compounds were adsorbed by the bacteria.—*The Influence of Surface-Active Substances on the Growth of Acid-fast Bacteria*, A. E. Alexander & N. A. Soltya, *J. Path. & Bact.*, January, 1946, 58: 57.—(H. J. Henderson)

Preservation of Tubercle Bacilli.—The object of this experiment was to ascertain the ex-

tent of resistance of *M. tuberculosis* (human and bovine types) to (a) freeze-drying and (b) storage at -76°C . Suspensions containing 1 mg. per 1 ml. were made in distilled water, physiological saline solution and in inactivated bovine serum, respectively. These suspensions were subjected to freeze-drying and to storage at -76°C . over a period of 180 days at seven-day intervals. An ampoule was diluted in serial dilutions ranging from $1:10^4$ to $1:10^8$ and inoculated into both guinea pigs and hamsters. The results of the biological test were checked by culturing the suspensions. Suspensions stored at low temperature showed no appreciable loss after 180 days. Freeze-dried material sustained an immediate fall in activity, estimated at 100 to 1,000 fold; thereafter the dried material remained stable. Bacterial suspensions preserved at -76°C . can be used with advantage in experiments where it is necessary to inoculate small numbers of living bacilli and to obtain reproducible results.—*The Effects of (a) Freeze-Drying and (b) Low Temperature on the Viability of Mycobacterium Tuberculosis*, R. E. Glover, *J. Path. & Bact.*, January, 1946, 58: 3.—(H. J. Henderson)

Submerged Growth of Tubercle Bacilli.—The new synthetic media of Dubos for the rapid cultivation of Mycobacteria can be successfully employed to isolate tubercle bacilli from various pathological material. A combination of rapid culture with guinea pig inoculation where indicated should result in a marked reduction of the time required for the laboratory diagnosis of tuberculosis.—*Submerged Growth of Tubercle Bacilli from Pathologic Material in Dubos' Medium*, G. E. Folcy, *Proc. Soc. Exper. Biol. & Med.*, June, 1946, 62: 298.—(F. B. Schbert)

Tubercle Bacilli in Bronchoscopic Aspirations.—Bronchoscopic aspiration of secretions is recommended as a method of improving bacteriological diagnosis. The importance of penetrating as deeply as possible into the lobar bronchi, especially of the upper lobes, is emphasized. With this method the authors have

succeeded in demonstrating the presence of tubercle bacilli four times out of five in cases of small pulmonary infiltrations which had been negative on repeated examinations including gastric lavage.—*Les prélèvements bronchiques dans la recherche du bacille de Koch*, M. Bariéty & J. Paillas, *Rev. de la tuberc.*, 1944-45, 9: 337.—(V. Leites)

Culture of Tubercle Bacilli.—Various methods for destroying contaminants are discussed. Search was made for a pure, stable, crystalline material which would allow time for preparation of the specimen and which might even be added to the specimen immediately on collection. Trisodium phosphate was the agent finally selected, in preference to several reagents, including oxalic acid and sodium hydroxide. Trisodium phosphate was used in 10 per cent solution, and it was found that it could remain in contact with tubercle bacilli up to a week at room temperature without destroying small numbers of tubercle bacilli. It was found that this reagent could be placed in receptacles for use in collecting tuberculous specimens and thus prevent the development of molds and contaminants. It was found that the time required for destroying contaminants by trisodium phosphate is one day at 37° C.—*An Improved Procedure for the Diagnostic Culture of Mammalian Tubercle Bacilli*, H. J. Corper & R. E. Stoner, *J. Lab. & Clin. Med.*, December, 1946, 31: 1364.—(R. W. Clarke)

Growth Stimulation of Tubercle Bacilli.—The growth of mycobacteria on four kinds of egg media was observed: Dorset's (whole egg), egg-yolk, egg-white and a "defatted" yolk medium. A constant amount of inoculum was added to each of the media. Growth was observed from four to seventy days after inoculation. The amount of growth was determined by comparison with the growth on whole egg medium. Saprophytic acid-fast bacteria and those mycobacteria which are pathogenic for cold-blooded animals (excepting *M. marinum* Aronson and *M. tuberculosis*, Cayman strain) grew moderately well on egg-

white but did not attain the standard of growth characteristic of whole egg medium. *M. phlei* and *M. ranae* also grew moderately well on the "defatted" yolk medium. Avian, bovine and human tubercle bacilli exhibited no growth on egg-white and "defatted" yolk media at a time when luxuriant growth had been obtained on whole egg medium. All the organisms grew faster on the yolk medium. *M. tuberculosis hominis* (H37) produced scant growth on egg-white medium after ten weeks' incubation. The addition of purified oolecithin and of ether soluble yolk lipids to egg-white medium stimulated the growth of *M. phlei*, *M. smegmatis*, *M. stercosis*, *M. karlinski*, *M. ranae*, *M. marinum*, *M. tuberculosis*, (Cayman strain) *M. tuberculosis hominis* (T₁), and *M. avium* (T₂). The addition of sodium citrate, asparagine, calcium, iron, dl-alanine, creatine, phthiocol, choline, ethanolamine, sodium palmitate, sodium stearate, sodium oleate, sodium glycerophosphate, ascorbic acid, nicotinamide, pyridoxin, pantothenic acid, riboflavin, dl-lactate and cytochrome to egg-white medium failed to stimulate the growth of tubercle bacilli. A crude phosphatide fraction of egg-yolk stimulates the growth of tubercle bacilli.—*Stimulation of the Growth of Egg Yolk*, Margaret K. Finlayson, *J. Path. & Bact.*, January, 1946, 58: 88.—(H. J. Henderson)

Diagnostic Culture of Tubercle Bacilli.—The reagents commonly used for destroying contaminants are sodium hydroxide, sulfuric, hydrochloric and oxalic acid. These reagents are harmful to small numbers of tubercle bacilli even after two hours' exposure. A 10 per cent solution of chemically pure trisodium phosphate (equivalent to 23 per cent of Na₃PO₄·12H₂O) added to fine suspensions of mammalian tubercle bacilli proved not only innocuous to the bacilli but was more protective than suspension of the bacilli in 0.9 per cent saline solution for long periods. This reagent destroys contaminants in one day at 37° C. or within several days at room temperature. It can remain in contact with tubercle bacilli for up to a week at room temperature

without destroying small numbers of tubercle bacilli. One week's exposure at 37° C. was not particularly detrimental to the viability of the tubercle bacilli, although the longer interval of one week's contact retards their growth. It was noted that either neutralization or washing out the phosphate produces more satisfactory results when compared with their planting in the phosphate as such. Glycerol egg-yolk medium when properly prepared proved the most efficient medium.—*An Improved Procedure for the Diagnostic Culture of Mammalian Tubercle Bacilli*, H. J. Corper & R. E. Stoner, *J. Lab. & Clin. Med.*, December, 1946, 31: 1364.—(F. G. Petrik)

Vole Tubercle Bacilli.—It has been shown previously that vole tubercle bacilli are only slightly pathogenic for rabbits and guinea pigs. Injection of caseous material from lesions of naturally infected voles or of living vole tubercle bacilli protects these animals against virulent mammalian tubercle bacilli. Pathogenicity of the vole organism for calves is low. Its immunizing power is greater than BCG. All calves develop strongly positive tuberculin reactions. In the current study, 16 patients with far advanced tuberculosis were injected intracutaneously with 0.0001 mg. of a culture of living vole tubercle bacilli. A marked local reaction developed consisting of a tiny red papule surrounded by an area of erythema. This slowly increased in size, reaching its maximum size in ten days. In most, the papule became a pustule. There was no lymphadenopathy or constitutional reaction. The intensity of the reaction paralleled the Mantoux reaction. In other cases, the bacilli used were killed by heat; the reaction was slightly less intense but of the same character. When dosages up to 0.1 mg. were used, the same reactions were obtained but with intensity in proportion to the dosage scale. In no case was a patient affected adversely.—*The Intracutaneous Injection of Vole Tubercle Bacilli in Tuberculous Persons*, C. Cameron & I. A. Purdie, *Tubercle*, December, 1946, 27: 195.—(A. G. Cohen)

Codliver Oil in Tuberculosis.—Codliver oil administered intravenously at a rate of 3 cc. per kg. of weight causes no embolism. Two dogs of the same age and weight, one of which received an intravenous injection of virulent tubercle bacilli at the outset of the study, were treated with intravenous injections of codliver oil at the above rate for two months. Both animals survived, but the noninfected one weighed 1.5 kg. more than the one that was infected. Two goats were inoculated with virulent tubercle bacilli and one of them was treated with codliver oil injections in the above manner. Both animals were infected, but only one was treated. The nontreated goat died forty days after the injection, while the animal that was treated lived twenty days longer. No general conclusions can be drawn from these preliminary experiments; it appears, however, that codliver oil used in experimental tuberculosis increases the resistance to infection and diminishes the virulence of the bacilli.—*Ensayo de tratamiento de la tuberculosis experimental con aceite de higado de bocolao endovenoso*, S. Gutman, *Prensa méd. argent.*, August, 1946, 33: 1641.—(L. Molnar)

Tuberculosis in Hamster.—A series of experiments was undertaken to determine the smallest dose of virulent human and bovine bacilli capable of infecting the hamster and to compare the susceptibility of this species with that of the guinea pig. Suspensions of seven to ten-day-old cultures, grown on Herrold's glycerol egg agar were inoculated subcutaneously. Serial dilutions ranging from 1:10,000 mg. to 1:100,000,000 were used. The golden hamster is as susceptible as the guinea pig to the subcutaneous inoculation of the human and bovine types of *M. tuberculosis*. In each species the minimal infective dose of a fully virulent bovine strain is 1:10⁷ mg. bacilli; the corresponding dose of the human type is 1:10⁶ mg. In the hamster, caseous lesions are not common. A proliferative adenitis in which the nodes were teeming with acid-fast bacilli was noted.—*Susceptibility of the Golden Hamster (Cricetus Auratus) to Mycobacterium*

Tuberculosis Hominis and Bovis, R. E. Glover, *J. Path. & Bact.*, January, 1946, 58: 107.—(H. J. Henderson)

Tuberculous Necrosis.—Necrotic tuberculous lesions were examined histologically, bacteriologically and biochemically. Numerous references to the literature on tuberculous necrosis and caseation are given. The authors do not believe that the fats contained in foci of caseous necrosis are due to sources outside the lesion or to fatty infiltration. Tuberculous necrosis is considered a tissue disintegration. Its biochemical constituents result from the transformation of normal tissue elements. No correlation could be found between the extent of necrosis and the quantity of demonstrable bacilli. More bacilli were found in foci of "incomplete" necrosis containing nuclear debris than in "complete necrosis." Foci of liquefied necrosis were always extremely rich in bacilli, apparently indicating a parallelism between bacillary content and content in leucocytes. It is the opinion of the authors that necrosis develops only in exudative lesions. Whenever productive foci show necrotic transformation these foci are assumed to have been the site of an associated exudative reaction. Tubercle bacilli are not believed to cause necrosis by direct fermentative action. Their rôle is rather seen in an indirect catalytic effect. No fundamental differences could be demonstrated between foci of dry and liquefied necrosis regarding the nature and the quantity of the fatty substances which they contain. The softening of a tuberculous lesion is attributed to phenomena occurring in the surrounding tissue, in particular to the state of perifocal circulation. Aqueous inhibition of the necrotic area is the result of exudation from perifocal vessels with migration of leucocytes. The marked increase in bacillary content during the stage of liquefaction is considered secondary to these "unspecific" processes of perifocal exudation.—*Signification biologique des divers aspects de la necrose tuberculeuse*, F. Besançon & J. Delarue, *Rev. de la tuberc.*, 1946, 10: 9.—(V. Leites)

Persistence of Tuberculin Sensitivity.—Negative tuberculin reactions in persons with calcified foci in the lung or tracheobronchial lymph nodes might be due to obsolete tuberculous residues which no longer elicit hypersensitivity, or the calcified areas may have resulted from nontuberculous origins such as coccidioidomycosis, histoplasmosis etc. To determine what percentage of cases with tuberculin hypersensitivity become anergic Hardy studied 312 persons who had a primary tuberculosis during childhood. She found that of 59 persons who had the more severe types of lesion, none became anergic more than fourteen years after their primary infection. Of 171 persons with mediastinal tuberculosis, whose hypersensitivity was less marked than that of the first group, 2 per cent became anergic to 1 mg. of tuberculin. Of 82 persons who reacted to tuberculin but who had no demonstrable X-ray evidence of tuberculosis at the beginning of the study, 6 per cent became anergic. These persons were not in contact with sputum positive cases and only one developed reinfection tuberculosis after the healing of the primary lesion. From these data the author concludes that, though tuberculosis may be the etiological factor of calcified lesions which are not accompanied by hypersensitivity to 1.0 mg. of tuberculin, this occurs but rarely. Hence most of the calcified lesions unaccompanied by hypersensitivity are probably of a nontuberculous nature.—*Persistence of Hypersensitivity to Old Tuberculin following Primary Tuberculosis in Childhood*, Janet B. Hardy, *Am. J. Pub. Health*, December, 1946, 36: 1417.—(M. B. Lurie)

Cellular Transfer of Tuberculin Reactivity.—Guinea pigs were rendered hypersensitive to tuberculin by subcutaneous injection of killed human tubercle bacilli suspended in paraffin oil. Between five and nine weeks later, exudate cells were collected and washed and immediately injected into guinea pigs. In about forty-eight hours tuberculin hypersensitivity became established in the cell recipients and maximal reactivity occurred in seventy-two to ninety-six hours. Of 17 experiments

successful transfer of hypersensitivity occurred in 16 instances. The intensity of the transferred hypersensitiveness varied with the amount of cells used and the degree of sensitivity of the cell donors. The cells become inactive upon being heated at 48° C. for fifteen minutes or upon freezing or storing overnight in the ice-box. Cells from the spleen or lymph nodes, as well as exudate cells from the peritoneal cavity, are capable of transferring hypersensitiveness to Old Tuberculin.—*The Cellular Transfer of Cutaneous Hypersensitivity to Tuberculin*, M. W. Chase, *Proc. Soc. Exper. Biol. & Med.*, June, 1945, 59: 134.—(F. B. Seibert)

Accelerated Sensitization.—In 83 girls aged 14 to 21, tuberculin tests, performed nine days after the administration of BCG, remained completely negative except in 3 who had been previously doubtful. Almost all became positive before another ten weeks. Although there is no evidence that any of these girls had ever been actually infected and later spontaneously desensitized, the authors conclude that the absence of accelerated sensitization following infection in the human cannot be accepted as proof that the subject has never been previously infected.—*Le phénomène de Baldwin-Gardner-Willis chez le cobaye et chez l'homme*, P. Boulenger & A.-C. Maclouf, *Rev. de pathol. comp. et d'hygiène gen.*, January-February, 1944, p. 87.—(E. Bogen)

BCG Vaccination.—BCG vaccination by means of the multiple puncture technique is asserted to have been entirely innocuous both locally and generally in animals studied over a period of ten years and in infants studied over a period of seven years. In 1,302 vaccinated children there were 4 cases of tuberculosis and one death from the disease, while in 1,276 controls there were 27 cases of tuberculosis and 7 deaths. The greater danger for children exposed to tuberculosis than in those where no contact is known is seen in both vaccinated and controls. It is concluded that in the first seven years of life BCG vaccination is of definite value in the prevention of tubercu-

losis.—*Ten Years Experience with BCG (Experimental and Clinical)*, S. R. Rosenthal, Margery Bland & Eleanor I. Leslic, *J. Pediat.*, May, 1945, 26: 470.—(E. Bogen)

BCG Vaccination.—Administration of BCG by means of multiple scratches through the vaccine deposited on the skin resulted in 95.5 per cent positive tuberculin reactions in 89 girls tested within the next ten weeks. Sensitization developed earlier and stronger when the total length of the scratches was greater than 12 cm. than when it was less than 7 cm.—*Le BCG par scarifications cutanées*, A. Courcoux, P. Boulenger & A.-C. Maclouf, *Rev. de pathol. comp. et d'hygiène gen.*, September-October & November-December, 1944, p. 39.—(E. Bogen)

Local Reactions to BCG.—The local reactions to BCG applied by intracutaneous injection or by scarification in the new-born and in tuberculin-negative persons consist in the appearance of very small nodules eight to twenty-one days after the administration and their disappearance a few weeks later without leaving a scar. The local reactions of BCG in adults with or without tuberculosis were studied. Generally speaking, the local reaction to BCG was found parallel to the tuberculin reaction, but much more intense than the latter. In particular, BCG provokes frequently suppuration which is not observed in tuberculin reactions. The local reaction to BCG in tuberculous patients appears early. A papule develops on the first or second day after administration. The reaction is at its maximum on the fifth day consisting in vesiculation and suppuration; scar formation occurs at the end of the third week. In a second series of patients in the terminal stage of tuberculosis with negative or slightly positive tuberculin reactions, BCG did not produce any local reactions in most cases.—*Réactions locales produites par le BCG inoculé par scarification chez les malades tuberculeux*, L. Corre, *Ann. Inst. Pasteur*, May-June, 1946, 72: 441.—(V. Leites)

History of Penicillin.—It is pointed out that an Italian, B. Gosio, isolated an antibiotic substance from some species of penicillium in 1896, that Lieske in Germany rediscovered such a substance in 1921 and that Gratia and Dath, in Belgium, reported a similar substance in 1924. The Belgian authors treated patients with furunculosis with such a substance as early as 1927 and stated that "It is the most effective treatment, even of the most resistant types of staphylococcal diseases."—*The First Discoverers of Penicillin and of Its Application in Therapy*, J. T. Peters, *Acta med. Scandinav.*, 1946, 126: 60.—(M. Pinner)

Bacteriostasis in vitro.—Twenty-nine different compounds were examined *in vitro* for their tuberculostatic activity. The drugs were mixed in various concentrations with a slightly modified Dorset medium, and the media were inoculated with a standardized quantity of a highly virulent strain of human tubercle bacilli (AT); after twenty-eight days of cultivation the known weight of the bacillary growth was compared with the known weight of the seeded bacilli. P-aminobenzoic acid, an essential metabolite of the tubercle bacillus, destroys the bacteriostatic action of sulfanilamides; it had no influence on the normal growth of the tubercle bacilli in the concentrations employed in these experiments. Of all the substances studied, sulfathiazole had the greatest tuberculostatic action. A new derivative of sulfapyridine abolished the bacteriostatic action of this drug. Sulfanaphthoquinone has a pronounced tuberculostatic effect. It was used because a naphthoquinone has been obtained from the tubercle bacillus and is essential for the growth of another acid-fast bacillus. Two other naphthoquinone compounds were ineffective. 4,4'-diaminophenylsulfone was highly active. Its derivatives, diasone and tibatin, were less effective, and then only in so far as they were converted into the parent substance. Good results were obtained with a hydroxythiazolyle sulfone, a derivative of promizole. Promizole itself had no definitive effect, and a few other of its derivatives were only moderately active.

4-amino-methylsulfanilamide, the bacteriostatic action of which is not inhibited by P-aminobenzoic acid, was active in high concentrations. On account of the affinity of several vital stains for the tubercle bacillus a number of triphenylmethyl-substituted sulfanilamides were synthesized but showed no activity in the concentrations obtainable. Iodinine has a strong inhibitory effect on streptococci, which can be eliminated by certain quinones. In the high dilutions that could be obtained it had a definite effect on tubercle bacilli. A quinoxaline-di-N-oxide had a moderate action. Urea and thiourea were ineffective, while thioracil was slightly active. Sulfanilacetophenone was somewhat tuberculostatic; sulfanilacetone was inactive.—*Tuberculostatic Activity in vitro of Twenty-nine Different Compounds (Sulfanilamides, Naphthalene and Tritane Derivatives of Sulfanilamide, Diaminodiphenylsulfones, Derivatives of Promizole, Iodinine and Some Others)*, A. R. Frisk, *Acta med. Scandinav.*, 1946, 125: 487.—(O. Pinner)

Antagonistic Growth Substances.—Substitution of an SO_3H or SO_2NH_2 radical for the COOH in certain growth promoting compounds has been shown to produce antagonistic, or bacteriostatic, effects. Asparagine, the amide of aspartic acid, is known to favor growth of tubercle bacilli. Theoretically, then, by substituting an SO_3H (or SO_2NH_2) radical for one of the carboxyl radicals in asparagine, a bacteriostatic may be obtained. Cysteic acid (2-amino 3-sulfonic propionic acid) synthesized first by Friedmann in 1903, is the resulting compound and has been shown to inhibit growth of *S. aureus*, *B. coli* and proteus bacilli, although heretofore no work has been done with this agent in connection with the tubercle bacillus. Experimental work with cysteic acid added to Sauton's medium, with and without asparagine, demonstrated the validity of this induction: cysteic acid does vitiate the favorable effect of asparagine when used in equal molecular concentration with asparagine; when used alone, measurable bacteriostasis obtains. Cysteic acid appears to diminish bacillary proliferation

in proportion to the *log.* of its concentration. Sulfolactic acid ($\text{COOH}\cdot\text{CHOH}\cdot\text{CH}_2\cdot\text{SO}_3\text{H}$), obtained from cysteic acid by the substitution of an OH for the NH_2 radical, is equally effective in inhibiting growth of tubercle bacilli.—*Influence antagoniste de l'asparagine et de l'acide cystéique sur la croissance du bacille tuberculeux humain*, E. Perdigon, F. Bouquet, M. T. Mazaudier & F. Godard, *Ann. Inst. Pasteur*, July–August, 1946, 72: 573.—(P. Q. Edwards)

Chemical Inhibition of Bacilli.—The activity conferred upon a given organic nucleus by the addition of various radicals has been the subject of the present paper. A culture of avian tubercle bacilli on Sauton's medium is not influenced by benzene, but the amine of benzene, that is, aniline, is active in 1:1,000. Aniline derivatives obtained by substitution, for example acetanilide, were found to be inactive; addition of an NO_2 group appears to enhance the inhibitory action; addition of a second NH_2 group also increases inhibitory activity considerably. Phenol is active in 1:2,000 concentration; alcylation in certain positions increases this activity. Benzoic acids and their derivatives are, as a group, practically inactive. Benzaldehyde, active in 1:1,000, is further activated by nitration, especially in the ortho and meta positions. Naphthalene has no action *in vitro* on Koch's bacilli, yet by introduction of an amine radical in the β position considerable activity is produced. Double nitration further enhances activity. Derivatives of organic metallic compounds, such as phenylarsinic acid, show some activity; hydrazines are more active. Urea, sulfoxides, sulfones, amines, quinones, pyridines, chaulmoogra acids and divers substances are cited with relation to their inhibitory activity. Of all the above compounds, the amines, aldehydes and nitrated derivatives appear to possess the most inhibitory activity against Koch's bacillus.—*De l'activité inhibitrice des représentants de quelques séries chimiques sur la pousse du bacille de Koch*, J.-P. Jouin & Buu-Hoi, *Ann. Inst. Pasteur*, July–August, 1946, 72: 580.—(P. Q. Edwards)

Tuberculostatic Substances.—The compound 5-amino-2-butoxy pyridine and its least toxic derivative, a sodium formaldehyde bisulfite compound, proved to be bacteriostatic *in vitro* for 607, the rapidly growing strain of tubercle bacillus, as well as for virulent and recently isolated strains, but not for other species of bacteria. The bacteriostatic activity of these compounds against the tubercle bacillus was not antagonized by para-amino-benzoic acid, methionine, riboflavin, calcium pantothenate, adenine, guanine, thiamine, uracil, nicotinic acid, biotin, culture filtrates from staphylococci, pneumococci and tubercle bacilli, pus from streptococcal lymphadenitis, constituents of beef culture, media, peptone, whole blood and serum up to 25 per cent. It is suggested that the mechanism of action involves the interference with some essential metabolic process common to species of *Mycobacterium* but not to other genera of organisms.—*A New Class of Tuberculostatic Substances*, W. H. Feinstone, *Proc. Soc. Exper. Biol. & Med.*, October, 1946, 63: 153.—(F. B. Seibert)

Antibiotic from *Ramalina Reticulata*.—A crystalline substance was isolated from *Ramalina reticulata*, sometimes called California Spanish moss, which is a lichen. The methods of isolation are described, as well as some of the chemical and physical characteristics of this crystalline material. *In vitro* experiments showed that this substance has antibacterial properties; in a concentration of 50 gamma per cc. of medium, it completely inhibited the growth of some pneumococci and streptococci. Human strains of tubercle bacilli were completely inhibited by concentrations of 1:50,000 and some inhibition occurred at concentrations as low as 1:2,000,000. The bovine strain, Ravenel, was inhibited by a concentration of 1:20,000. The substance could be administered to both normal and tuberculous guinea pigs without obvious toxic effects. In the few animal experiments reported, it was established that this substance inhibited experimental tuberculosis to a marked degree, as shown by weight, mortality, extent and characteristics of the tuberculous lesions in treated

animals.—A *Crystalline Antibacterial Substance from the Lichen Ramalina Reticulata*, A. Marshak, *Pub. Health Rep.*, January 3, 1947, 62: 3.—(M. Pinner)

Streptomycin in Tuberculosis.—In the past two years 100 patients with various types of tuberculosis were treated with streptomycin. Twelve patients had generalized hematogenous tuberculosis, 9 of them with clinical evidence of meningitis. Six of these 12 patients died. Five of the surviving patients have been observed for from two to ten months; 4 of them had tuberculous meningitis. Symptomatic improvement was observed within one or two weeks after the treatment was begun. It has been impossible to demonstrate tubercle bacilli in the cerebrospinal fluid after several weeks of treatment. Changes in the spinal fluid to nearly normal occurred in 2 patients. Residual neurological disturbances are present in 3 of the 4 patients. The treatment consisted of the intrathecal administration of 100 to 200 mg. of streptomycin every twenty-four to forty-eight hours for two to six weeks. In addition, they received 2 to 3 g. of streptomycin by intramuscular injection for six months. None of the patients who died had received intrathecal therapy. Clinical, roentgenographic and histopathological evidence of healing trends were observed in miliary tuberculosis but actual cure was not witnessed. Thirty-two patients with active, usually progressive, nonsurgical tuberculosis of the lungs in which rapid, spontaneous improvement was not likely to occur were treated with streptomycin. Twenty-one patients had far advanced, 9 moderately advanced and 2 minimal disease. Definite roentgenographic improvement was observed in 25 patients. In 12 patients cavities closed, in 6 patients thick walled cavities persisted, in the rest cavities were not demonstrable. In 13 patients spu-

tum conversion was observed, 15 patients remained positive. No progression of the pulmonary lesions was noted during the treatment. Five patients died. After the discontinuation of treatment, reactivation occurred in 6 patients, one of them developed a streptomycin-resistant strain of *Mycobacterium tuberculosis* at the time of reactivation. Five patients with ulcerating lesions of the respiratory passages showed prompt improvement following treatment with streptomycin. Tuberculous empyema treated by intramuscular or intrapleural (or both) administration of streptomycin showed improvement only in one out of 7 cases. Fifteen patients with various types of tuberculous fistulae responded favorably to streptomycin within four to six weeks. Streptomycin had only palliative value in the treatment of 15 patients with tuberculous cystitis. Four patients with tuberculosis of bones and joints responded to treatment with streptomycin. In 7 patients surgical measures in the treatment of pulmonary tuberculosis were combined with streptomycin therapy with seemingly good results. The dosage of streptomycin was 1 to 3 g. per twenty-four hours divided in 4 to 6 doses. The solution consisted of 100 to 250 mg. of streptomycin in 1.0 cc. of sterile water. Aerosol spray consisted of 20 cc. of isotonic solution of sodium chloride which contained 0.5 g. of streptomycin; 2 cc. were nebulized each hour for ten hours of the day. The most frequent reaction caused by streptomycin was disturbance of equilibrium. In many instances streptomycin appeared to suppress tuberculosis rather than to eradicate it. It is not to be regarded as a substitute for other and proved effective forms of treatment of tuberculosis.—*Treatment of Tuberculosis with Streptomycin: A Summary of Observations on One Hundred Cases*, H. C. Hinshaw, W. H. Feldman & K. H. Pfuetze, *J. A. M. A.*, November 30, 1946, 132: 778.—(H. Ables)

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Streptomycin in Tuberculous Meningitis.—Report of a case of tuberculous meningitis following hematogenous tuberculosis in a 4-year-old boy treated with streptomycin is given. Miliary infiltrations throughout both lung fields were seen in the admission film. Streptomycin 1.0 g. intramuscularly and 0.01 gm. intrathecally daily was begun on the fifth hospital day; doses were raised to 1.2 g. intramuscularly in divided doses every two hours and 0.1 g. intrathecally daily on the ninth day. Because of red cells in the spinal fluid and a persistent febrile reaction, the drug was stopped after a total of 85.0 g. intramuscularly and 3.0 g. intrathecally had been administered. Chest films six weeks after admission showed clearing of the disseminated lesions. Convulsions, strabismus and bacilli appeared again in the spinal fluid three months after entry and caused streptomycin to be again administered; the child died within the next month. No extrapulmonary source of the bacilli was located antemortem. During administration of the drug, the patient showed an apparent auditory neuritis on the eighteenth day, with a concomitant leucopenia. Septic fever and a miliary skin eruption were also observed. An acute diphtheritic pharyngo-tonsillitis developed during the streptomycin therapy; penicillin produced prompt clearing. Postmortem examination showed healing pulmonary tubercles, miliary splenic tubercles and a caseous parenchymal lesion in the brain directly continuous with a caseous exudate in the meninges.—*Streptomycin in Miliary Tuberculosis with Tuberculous Meningitis*, P. K. Bornstein, *Quart. Bull. Sea View Hosp.*, July, 1946, 8: 219.—(P. Q. Edwards)

Streptomycin in Tuberculous Meningitis.—A 15-month-old boy took sick with fever, irritability, restlessness and anorexia. A diagnosis of follicular tonsillitis was made and the child was treated with sulfadiazine and penicillin. After temporary improvement recurrence of the fever and restlessness was observed. Physical examination revealed nuchal rigidity and hyperactive knee jerks. Examination of the spinal fluid gave the following result: sugar, 15 mg.; chlorides, 460 mg.; positive Levinson test, pellicle formation on standing, acid-fast bacilli on direct smear. A chest film showed hilar enlargement, more marked on the right side. A tuberculin patch test was positive. The child received 24,000,000 units of streptomycin intramuscularly and 2,800,000 units intrathecally, over a period of fifty-seven days. The child recovered completely. The probable source case was the maternal grandmother who was treated for pleurisy at a tuberculosis hospital. Guinea pig inoculations with spinal fluid were done only after treatment with streptomycin had been started. They were negative for tuberculosis.—*Tuberculous Meningitis Treated with Streptomycin*, L. F. Krafchik, J. A. M. A., October 19, 1946, 132: 875.—(H. Abeles)

Streptomycin and Promin in Rat Tuberculosis.—Rats inoculated with a human strain of tubercle bacilli (A27) were treated with streptomycin and promin, individually and in combination, and the effect of treatment determined by (a) direct tissue smears, (b) subculturing of lung suspensions, (c) subinoculation of lung suspensions in guinea pigs. Treatment with promin alone showed no

beneficial effects. Treatment with streptomycin alone resulted in an average lower colony count than in the controls, while treatment with both drugs appeared to indicate sterilization of 41.6 per cent of the animals and marked decrease and attenuation of persisting viable tubercle bacilli in the remainder.—*Influence of Streptomycin and Promin on Proliferation of Tubercle Bacilli in the Tissues of Albino Rat*, M. I. Smith, W. T. McClosky & E. W. Emmart, *Proc. Soc. Exper. Biol. & Med.*, June, 1946, 62: 157.—(F. B. Seibert)

Inactivation of Streptomycin.—The antibacterial activity of streptomycin can be largely or completely neutralized or antagonized by glucose and certain other sugars, an anaerobic environment, certain sulfhydryl compounds, and ketone reagents. In some cases, the effect can be traced to the acidity produced. In the effect of cysteine, cevitamic acid, and of ketone reagents the inhibition of streptomycin activity may be associated with the blocking of an active grouping in the molecule of the streptomycin.—*The Inactivation of Streptomycin, and Its Practical Applications*, W. B. Geiger, S. R. Green & S. A. Waksman, *Proc. Soc. Exper. Biol. & Med.*, February, 1946, 61: 187.—(F. B. Seibert)

Streptomycin Resistant Strains of Tubercle Bacilli.—Streptomycin resistant human type tubercle bacilli were found to be as virulent for white mice as streptomycin sensitive strains. Infection produced in mice with these streptomycin resistant cultures was not suppressed by treatment of the mice with streptomycin.—*Effect of Streptomycin on Experimental Infections Produced in Mice with Streptomycin Resistant Strains of M. tuberculosis var. Hominis*, G. P. Youmans & Elizabeth H. Williston, *Proc. Soc. Exper. Biol. & Med.*, October, 1946, 63: 131.—(F. B. Seibert)

Absorption and Excretion of Streptomycin.—Streptomycin is rapidly absorbed and excreted following parenteral administration.

The rapid disappearance of streptomycin from the blood is largely accounted for by its early appearance in the urine. Approximately 60 to 80 per cent of the drug is excreted in the urine of dogs within a twenty-four-hour period after parenteral administration. Somewhat smaller amounts were excreted in the urine of monkeys. When the drug is given perorally relatively small amounts are detected in the blood. This is largely due to the lack of absorption of streptomycin from the gastro-intestinal tract, as shown by the large amount of the drug recovered in the feces. Therapeutic blood concentrations can be maintained by repeated intramuscular injection. Following intravenous administration of streptomycin only 5 to 10 per cent of the dose can be demonstrated in the bile.—*Studies on the Absorption and Excretion of Streptomycin in Animals*, R. B. Stebbins, O. E. Graessle & H. J. Robinson, *Proc. Soc. Exper. Biol. & Med.*, October, 1945, 60: 68.—(F. B. Seibert)

Cytotoxicity of Streptomycin and Streptothricin.—Several different preparations of streptomycin were tested on cultures of rabbits spleen and were found to have a uniformly low toxicity for wandering cells and fibroblasts. Streptothricin had a relatively low cytotoxicity for leucocytes and macrophages but showed a fairly high cytotoxicity for fibroblasts.—*Cytotoxicity of Streptomycin and Streptothricin*, Dorothy H. Heilman, *Proc. Soc. Exper. Biol. & Med.*, December, 1945, 60: 365.—(F. B. Seibert)

Streptomycin in Body Fluids.—With the use of a streptomycin sensitive organism (*Staphylococcus aureus* SM), which was not inhibited by normal blood, by increase of pH of the medium, or by decrease in salt concentration, and a technique similar to that used for penicillin, it was possible to assay streptomycin in the blood, urine, tissue fluids of mice, rats, rabbits, dogs, monkeys and man.—*A Method for Determination of Streptomycin in Body Fluids*, R. B. Stebbins & H. J. Robinson, *Proc. Soc.*

Exper. Biol. & Med., June, 1945, 59: 255.—
(F. B. Seibert)

p-Aminosalicylic Acid for Tuberculosis.—Data are given on the concentrations of various amino- and hydroxy-derivatives of benzoic acid which inhibit the growth of the tubercle bacillus *in vitro*. Of 60 compounds tested, 2-hydroxy-4-aminobenzoic acid (p-aminosalicylic acid, "PAS") was the most active, having bacteriostatic action in concentrations as low as $10^{-5.5}$ molal. Mice, rats and rabbits tolerated PAS well when fed 5 per cent of the compound in their food. Guinea pigs became emaciated, lost hair, and died in one to two weeks or less, nevertheless PAS had some protective action in animals injected intraperitoneally with 3 mg. of virulent human tubercle bacilli. PAS appeared to delay or arrest the progress of tuberculosis in some human cases. It was usually given by mouth in doses of 5, 3, 3 and 3 g. at four-hour intervals during the day. Owing to its rapid elimination from the body, the blood levels of PAS varied greatly, but usually averaged 3 to 6 mg. per 100 cc. of blood. Benzocaine and cycloform (the ethyl and isobutyl esters of p-aminobenzoic acid) were nearly as tuberculostatic *in vitro* as PAS, and might be useful in the local treatment of painful tuberculous lesions such as laryngeal tuberculosis. PAS has only a bacteriostatic action against the tubercle bacillus, but appears to be a useful drug.—*Chemotherapy of Tuberculosis: The Bacteriostatic Action of p-Aminosalicylic Acid (PAS) and Closely Related Substances upon the Tubercle Bacillus, together with Animal Experiments and Clinical Trials with PAS*, J. Lehmann, *Svenska läk.-tidning.*, August, 1946, 43: 2029.—(W. C. Tobie)

p-Aminosalicylic Acid against Various Bacteria.—*Mycobacterium tuberculosis* (from sputum or from pure cultures) was grown in bouillon sealed on microscope slides by a method modified from that of Pryce (1941). The average concentration of p-aminosalicylic (PAS) which inhibited growth during

eight days' incubation in four experiments was 0.153 mg. per 100 cc. of bouillon (10^{-5} molal), agreeing well with the results of Lehmann, see preceding abstract. PAS did not modify the tuberculin reaction in guinea pigs. PAS was tested against 19 species (a total of 37 strains) of non-acid-fast bacteria (pathogenic and nonpathogenic) but there was no bacteriostasis with concentrations less than 1.25 to 2.50 per cent of PAS, at which concentrations, 13 strains gave no growth. PAS did not protect mice injected with pneumococci or with tetanus toxin.—*Experimental Trials of p-Aminosalicylic Acid (PAS) against Various Kinds of Bacteria*, O. Sievers, *Svenska läk.-tidning.*, August, 1946, 43: 2041.—(W. C. Tobie)

Clinical Experiences with p-Aminosalicylic Acid.—In treating tuberculosis, 4-aminosalicylic acid (p-aminosalicylic acid) (PAS) was usually given by mouth for three to four weeks, with one-week intervals without treatment. The daily dosage was 5, 3, 3 and 3 g., given at four-hour intervals. During treatment the average blood level was 5 mg. of PAS per 100 cc. of blood (extreme limits 1 to 10 mg.). In favorable cases, the fever usually gradually diminished over a period of days or weeks until the body temperature was normal. At the same time there was a reduction of the sedimentation rate, an increase in hemoglobin, a disappearance of tubercle bacilli from the sputum, an improvement in the roentgenological findings, and an increase in appetite. Relapses frequently occurred when treatment was suspended. The best results were obtained in exudative pulmonary tuberculosis, with 24 cases improved, 2 unimproved and 4 deaths. In productive fibrous cases, 9 improved, 7 did not improve and one died. Hilar tuberculosis (3 cases) and pleuritic tuberculosis (9 cases) showed improvement. Of 10 empyema pleurae cases (in some cases treated locally by injection of 5 to 10 per cent solutions of PAS without apparent benefit), 4 improved, 3 did not improve, and 3 died. However, extrapleural postoperative cavities

infected with *Mycobacterium tuberculosis* were treated very successfully by filling the whole cavity (usually of limited size) with a solution of PAS which was changed every second or third day. Healing resulted in 4 cases and improvement in 3 cases. Six cases of miliary tuberculosis or tuberculous meningitis terminated fatally despite treatment with PAS. PAS has a low toxicity. Toxic symptoms (seen in a few cases) were: kidney irritation with a slight albuminuria, diffuse gastrointestinal discomfort and occasionally troublesome diarrhea.—*Clinical Experiences in the Treatment of Pulmonary Tuberculosis with PAS*, G. Vallentin, *Svenska läk.-tidning.*, August, 1946, 43: 2047.—(W. C. Tobie)

Subtilin.—The antibacterial product, subtilin, obtained from *Bacillus subtilis* was found to be active chiefly against Gram-positive and also two Gram-negative bacteria, *Neisseria catarrhalis* and *N. gonorrhoeae*. Acid-fast organisms, including *Mycobacterium tuberculosis*, were also found to be susceptible to the antibiotic. The agent produced a bacteriostatic action in high dilution and a germicidal effect in greater concentration. A number of pathogenic higher fungi were also found to be susceptible to subtilin.—*Subtilin—An Antibiotic Produced by Bacillus subtilis: I. Action on Various Organisms*, A. J. Salle & G. J. Jann, *Proc. Soc. Exper. Biol. & Med.*, October, 1945, 60: 60.—(F. B. Seibert)

Action of *Bacillus subtilis*.—Experiments demonstrate definite bacteriostatic and bacteriolytic properties of *Bacillus subtilis* and of "endosubtilysine" on cultures of tubercle bacilli. Subcutaneous administration of endosubtilysine in guinea pigs with experimental tuberculosis produced a retardation in the progression of lesions.—*Action du bacille subtil et de l'endo-subtilysine sur le bacille de Koch (souche d'Arloing et Courmont) et dans la tuberculose expérimentale*, H.-R. Olivier & L. de Saint-Rat, *Rev. de la tuberc.*, 1946, 10: 50.—(V. Leites)

Toxicity of Subtilin to Embryonic Tissue.—Subtilin, an antibiotic extracted from *Bacillus subtilis*, which was found to be antagonistic chiefly against Gram positive organisms, including *Mycobacterium tuberculosis* and other acid-fast bacteria, showed an extremely low toxicity for embryonic chick heart tissue fragments cultivated *in vitro*. Subtilin was found to be approximately twenty times more toxic to *Staphylococcus aureus* than to chick heart tissue, a remarkably low tissue toxicity. A unit of subtilin is defined as the amount contained in 1 cc. of the highest dilution capable of killing *Staphylococcus aureus* in ten minutes at 37° C. (F.D.A. phenol coefficient method.)—*Subtilin—Antibiotic Produced by Bacillus subtilis: II. Toxicity of Subtilin to Living Embryonic Tissue*, A. J. Salle & G. J. Jann, *Proc. Soc. Exper. Biol. & Med.*, January, 1946, 61: 23.—(F. B. Seibert)

Tuberculosis in Swine.—Lesions classified as representative of tuberculosis in swine were examined by direct smears made from 102 submaxillary and mesenteric lymph nodes of swine, by culture and smears made from cultures with definite or suspicious growth, and by subcutaneous inoculation into chickens and guinea pigs. The chickens and guinea pigs did not react to avian and bovine tuberculin before inoculation. They were tested at about monthly intervals thereafter for about six months. Acid-fast bacilli resembling tubercle bacilli were found in smears from 95 (93.1 per cent) lesions. On culture, growth was obtained from 52 (50.9 per cent) of the lesions. The bacilli resembled tubercle bacilli, this being the only type encountered. From 15 (14.7 per cent) other lesions a few acid-fast bacilli were obtained on smears, but the number suggested that growth was either very slow or the organisms were carried over from the inoculum. As to the results of the inoculations into guinea pigs, only one swine specimen gave rise to generalized tuberculosis following guinea pig inoculation. Subinoculations in-

licated that this was a bovine type of tubercle bacillus. Quite a number of guinea pigs reacted slightly to avian tuberculin at one test or another; and 65 (63.7 per cent) had caseous lesions at the site of injection, revealing in all but one smear acid-fast bacilli resembling tubercle bacilli. Of the inoculated birds, 5 did not live long enough; of the remaining 97 birds, 85 (87.6 per cent) became either positive to tuberculin or contained acid-fast bacilli in their tissues. Only in 2 reacting birds was it impossible to demonstrate acid-fast bacilli. Four of 7 swine specimens, negative on smears for acid-fast bacilli, were infective for chickens, thus making a total of 99 (97 per cent) of the specimens containing acid-fast bacilli resembling tubercle bacilli. Two chickens, inoculated with swine specimens negative on culture in chickens and guinea pigs, died before a definite conclusion could be reached. Of the remaining 100 specimens, 4 were chicken-negative but gave rise to local lesions with acid-fast bacilli, that is, 89 (89 per cent) of the specimens were positive for tubercle bacilli by chicken and/or guinea pig inoculation. In 88 per cent, the avian type was apparently found, and in 1 per cent, the bovine type. In 11 (11 per cent) of the swine specimens a definite demonstration of viable tubercle bacilli was not possible by culture or animal inoculation, but in smears, acid-fast bacilli were present in all but 3. It is reasonable to assume that, in some instances, bacilli were of such low virulence or so few in number that they could not produce lesions in animals.—*Tuberculous Lesions of Swine: II. Survey of Lesions Found in the Prairie Provinces, Especially in Alberta*, J. C. Banker, *Canad. J. Comp. Med.*, September, 1946, 10: 250.—(O. Pinner)

Congo Red Test.—Interpretation of Congo red absorption tests falling between 40 and 90 per cent is equivocal. Bennhold declared that tests in this range indicate amyloid disease, the present work indicates the contrary. In a group of 73 patients tested

at Sea View Hospital and found to be within the "doubtful" absorption range (30 to 89 per cent), retesting revealed markedly inconsistent results, suggesting the possibility of a purely fortuitous factor in determining the exact percentage of dye absorbed. The retesting of these patients indicated that in no way may the test be considered to have prognostic value; a patient showing 80 per cent absorption now may have 40 per cent absorption in three months. No correlation exists between the values shown in the Congo red tests and the nature of the primary disease. Justifiable conclusions from this research are: a test showing less than 90 per cent absorption cannot be considered diagnostic of amyloidosis; minimal or moderate amyloid disease may exist in the 40 to 90 per cent group and must be distinguished by other diagnostic measures.—*The Significance and Interpretation of the "Doubtful" Congo Red Test*, I. J. Selikoff, *Quart. Bull. Sea View Hosp.*, July, 1946, 8: 194.—(P. Q. Edwards)

Congo Red Test.—A critical review and study of the existing methods of the Congo red test are given. The authors describe an improved technique. All patients in whom the Congo red in the plasma after four minutes was less than 15 mg. per thousand cc. were frankly amyloidotic. All those with 20 mg. or more, had no amyloidosis. As the distribution of the dye in the blood-stream is rapid and uniform, the four-minute test is generally sufficient. In liver disease the excretion of Congo red is slow. In nephrosis the excretion is rapid with presence of Congo red in the urine. In non-amyloidotic nephrosis, the disappearance of the Congo red is almost normal. There is not yet a satisfactory test for the recovery of Congo red in the urine.—*Técnica fotométrica para la dosificación del rojo congo del plasma sanguíneo en el diagnóstico de la amiloidosis*, A. J. Soubrie & A. Patalano, *An. Cáted. de pat. y clin. tuberc.*, June, 1945, 7: 143.—(W. Swienty)

Anatomy of Right Upper Lobe Bronchus.—The right upper lobe bronchus has four divisions: the apical branch, the anterior branch, the posterior branch, and the axillary branch. Bronchoscopic and anatomical studies of the orifice of the right upper lobe bronchus led to the following classification: orifice with three openings, orifice with four openings, orifice with two openings. In the majority of cases (72.5 per cent) the right upper lobe bronchus was found to have three openings leading into the apical, anterior, and posterior branches. The axillary branch originates from the anterior or posterior division or from both and is directed towards the point of junction of the three lobes. An orifice with four openings was found only in 10 per cent of cases. In these the axillary branch originates directly from the lobar bronchus. It is visible in the inferior part of the bronchoscopic field between the openings of the anterior and posterior branch and opposite the apical branch. An orifice with two openings was present in 15.5 per cent of cases, in which the apical branch originated from a common trunk with the anterior or posterior branch. The common trunk is always situated in the upper part of the bronchoscopic field. The axillary branch originates from the anterior or posterior branch or from both.—*Orifices bronchoscopiques et anatomie bronchique du lobe supérieur droit, H. D'Hour, Y. Devin & P. Langevin, Rev. de la tuberc., 1946, 10: 81.*—(V. Leites)

The Segments of Lung.—It seems expedient to define a bronchopulmonary segment as that portion of lung served by a principal branch of a lobar bronchus, and thus the branch may be called a segmental bronchus. Such branches are relatively constant. The anatomy of bronchi may be studied by casts, dissections and bronchograms. The surface limits of a segment may be studied by distending it with air through its bronchus. Collapse or infection may be limited to a segment. Intersegmental boundaries are often marked by partial fissures on the surface of the normal

lung. The radiological features of consolidation and collapse of each segment are described with a notation to the effect that, in nearly all so-called segmental consolidations, the radiographic shadow is smaller than would be expected from anatomical studies or inflation preparations. This is due to associated collapse. Proof of this lies in the presence of emphysema in adjoining segments, curving of interlobar fissures toward the shadow and compensatory displacement of the mediastinum or diaphragm. Conversely, there is nearly always some consolidation in a collapsed segment. There are nine major segments in the right lung and eight in the left lung. Levels of segmental boundaries are given with reference to a standard centering of the X-ray tube on the third costal cartilage at a distance of five feet. A segmental consolidation in the right middle lobe may be confused with interlobar effusion, but, in the lateral X-ray film, the fusiform homogeneous opacity of an effusion is absent. A bronchogram will usually distinguish between the two conditions by showing the relation of the middle lobe bronchus to the shadows. The most important application of segmental anatomy is the recognition of the fact that, where there is a segmental lesion, attention should be directed to the related bronchus where growth or stricture may be found. Thus, in bronchial carcinoma, an X-ray film revealing a large pulmonary opacity may be due not to growth but to consolidation or collapse due to growth in the affected bronchus. This will assist in estimating operability and in concentrating irradiation. In general, pneumonic lesions tend to transgress segmental boundaries or to affect less than a whole segment. This is especially true of atypical pneumonias. A truly segmental involvement is evidence against a simple pneumonic process. A knowledge of segmental anatomy with the direction of draining bronchi is important in planning postural drainage and in localization and external drainage of lung abscess. Acute putrid abscess is always segmental at its onset. Occasionally surgical resection

of separate bronchopulmonary segments is possible.—*The Segments of the Lung*, A. F. Foster-Carter & C. Hoyle, *Dis. of Chest*, November–December, 1945, 11: 511.—(K. R. Boucot)

Respiratory Air-flow.—The author has devised an instrument for measuring the instantaneous rate of air-flow during both phases of respiration. The instrument consists of a fine platinum wire suspended across the diameter of a tube. This wire is pivoted at one end and connected to a half-turn spring at the other. The wire is mounted in channels and, as air flows through the tube, the wire deflects in direct proportion to the rate of air-flow; this deflection is photographed on a moving film giving the air-flow curve or pneumotachogram. A portable instrument, operating upon a somewhat different principle, has been recently devised. Twenty-nine normal male subjects were tested with this portable instrument; similar curves were obtained in most of these patients. The curves obtained in bronchial asthma are diagnostic: the curves show marked damping especially in the expiratory phase; there is also a sharp return to zero at the end of expiration, a result produced in normal subjects by the application of external resistance. Among 8 patients with moderately advanced pulmonary tuberculosis, only 3 yielded abnormal curves; these 3 presented roentgen evidence of pulmonary fibrosis and diaphragmatic adhesions. First and early second-stage silicosis rarely produce any changes from the normal air-flow. Abnormal curves are usually seen in advanced second- and third-stage silicosis. The curves of 2 men with siderosis were within the normal range. Patients with chronic emphysema also manifested abnormal curves. Loss of pulmonary elasticity and internal resistance to air-flow are the chief factors in producing abnormal changes in air-flow curves. This technique appears to be of value in differentiating between lung deposits which cause fibrosis and those which produce X-ray changes without fibrosis.—*Respiratory Air*

Flow Characteristics and Their Relation to Certain Lung Conditions Occurring in Industry, L. Silverman, *J. Indust. Hyg. & Toxicol.*, September, 1946, 28: 183.—(H. R. Nayer)

New Method of Spirometry.—In order to avoid the disadvantages of the usual methods of bronchosprometry a new procedure is proposed based on compression of one hemithorax, thus permitting the evaluation of the function of each lung separately. A detailed description of the method is given, which combines thoracography, spirometry and hemithoracic compression. In cases where the patient does not tolerate complete blockage of the hemithorax, the method permits to vary the degree of compression. The institution of compression produces immediately a compensatory increase in the function of the contralateral lung, as evidenced by an increase of the amplitude of respirations. Even in cases of reduced or absent motility of one hemithorax due to pleural symphysis, fibrothorax or unexpandable lung, compression of the other side provokes a compensatory increase of the functional capacity—a fact which would not have become evident with the method of simultaneous bilateral bronchosprometry. The imperfections of the new method reside mainly in its technical difficulties, but it presents no discomfort for the patient.—*Une nouvelle methode d'examen fonctionnel separé des poumons*, P. Labesse, *Rev. de la tuberc.*, 1946, 10: 153.—(V. Leites)

Respiratory Centre.—The neurons which constitute the respiratory centre are diffusely distributed through the reticular formation of the caudal half of the bulb. Those in the ventral reticular substance overlying the inferior olivary nuclei are concerned with inspiration. Those in the dorsal reticular substance are concerned with expiration. Excitatory connections between the constituent neurons of a given centre provide for coördination of contraction of widely distributed respiratory muscles. Inhibitory connections between the two centres provide for

alternation of contraction of inspiratory and expiratory muscles. The neurons of the respiratory centre are sensitive to the chemical and physical constitution of their fluid environment. They are excited by impulses impinging upon them by way of collaterals of the major sensory and motor tracts. Under combined chemical and synaptic stimulation these neurons discharge impulses repetitively. The more intense the chemical stimuli and the more numerous the synaptic stimuli, the greater is the frequency of discharge of impulses and the greater is the number of neurons active. Since the inspiratory neurons have the lowest threshold, inspiration is the dominant phase of respiration. In the absence of inhibitory influences which act upon the inspiratory centre from without, its discharge is continuous, and maintained tonic inspirations or apneusis results. The depth of the apneusis is a function of the sum of all the stimuli acting upon the neurons of the inspiratory centre. Two inhibitory mechanisms operate to interrupt rhythmically this repetitive activity of the inspiratory centre, namely the vagal inhibitory mechanism and the pneumotaxic mechanism. As the lungs inflate during inspiration, impulses which originate in pulmonary stretch receptors and which travel centrally over afferent fibers of the vagus nerves excite the expiratory centre. The inspiratory centre is reciprocally inhibited and expiration results. As the lungs deflate, the afferent inflow diminishes, the inspiratory centre escapes and the cycle repeats. The pneumotaxic mechanism plays an analogous although a subsidiary rôle under most circumstances. Thus impulses originating in the inspiratory centre are transmitted rostrally to the pneumotaxic centre, and are then relayed caudally to the expiratory centre. Excitation of the expiratory centre leads to reciprocal inhibition of the inspiratory centre, whereupon the circuit ceases to function and the cycle repeats. When the vagus nerves are cut the pneumotaxic centre maintains the rhythm of breathing. The rhythm of breathing is impressed upon the respiratory centre by

inhibitory mechanisms operating from without, it is not an expression of properties inherent in the neurons of the centre. The depth of breathing is determined by the sensitivity of these neurons to their environment and by the excitatory influences exerted by the many afferents which impinge upon them. The rate of breathing is determined by the excitability of the neurons of the centre and by the activity of the inhibitory mechanisms which rhythmically interrupt their repetitive discharge. (Author's summary.)—*Organization of the Respiratory Center*, R. F. Pitts, *Physiol. Rev.*, October, 1946, 26: 609.—(G. C. Leiner)

Pulmonary Ventilation and Anoxemia.—The relation of pulmonary ventilation to arterial oxygenation has been studied in 9 resting subjects breathing 10.5 per cent oxygen. Arterial oxygen saturation was found to be extremely sensitive to even small changes in pulmonary ventilation. Increasing the resting ventilation by half, a change of which the subject is scarcely aware, may increase arterial saturation by 10 to 20 per cent. Doubling or tripling the resting ventilation produces smaller increases in saturation. Arterial oxygen tension bears a direct and linear relation to respiratory minute volume. With increasing ventilation the alveolar and arterial oxygen tensions increased 1.5 and 2.0 times as fast as the corresponding carbon dioxide tensions fell. Considerable improvement in oxygenation may be obtained, without symptoms of acapnia, by a small increase in resting ventilation. This effect is due to improved mixing of tracheal and alveolar air, replacement of carbon dioxide by oxygen and temporary elevation of the respiratory quotient, while subjects are in an unsteady state. The influence of changes in pulmonary ventilation must be evaluated in any clinical application of anoxia. (Author's summary.)—*The Effect of Pulmonary Ventilation on Anoxemia*, C. S. Houston, *Am. J. Physiol.*, July, 1946, 146: 618.—(G. C. Leiner)

Pulmonary Volume Receptors.—The responses of single afferent fibers of the vagus nerve to changes in lung volume were recorded in cats under Dial anesthesia. The fibers could be divided into distinct groups according to the rate at which their end-organs adapted to lung inflation. The slowly adapting receptors had on the average a lower inflation threshold than the rapidly adapting receptors. Some receptors of both kinds responded to forced deflation of the lungs, but none were found which responded only to deflation. The conduction velocity, measured in 20 fibers and corrected to body temperature, was between 8 and 44 meters per second. The differences in adaptation and threshold of the two afferent fiber groups when compared with the two reflexes evoked by inflation of the lungs, suggest that impulses from slowly adapting endings inhibit inspiration, while those from the rapid adaptors excite inspiration. This evaluation of function adequately accounts for the respiratory responses to both inflation and deflation of the lungs. Only the slowly adapting fibers are in action in eupnea. A change in their threshold contributes to the increased rate of respiration in hyperpnea. The principal function of the rapidly adapting fibers appears to be a reinforcement of depth of certain deep inspirations which have been initiated through other mechanisms. (Authors' summary).—*A Unitary Analysis of Pulmonary Volume Receptors*, G. C. Knowlton & M. G. Larrabee, *Am. J. Physiol.*, September, 1946, 147: 100.—(G. C. Leiner)

Alveolar Gas Pressure.—The limitations inherent in direct methods for sampling alveolar air become critical during experiments on exercising subjects. An indirect method for calculating alveolar gas pressures has been devised which requires simply the determination of arterial $p\text{CO}_2$ and $p\text{O}_2$ and $p\text{CO}_2$ of inspired and expired air. A theoretical analysis indicates that alveolar gas pressures so determined represent the physiologically effective mean pressures and are not subject to errors introduced by

"time" and "space" factors. By this indirect method the effective alveolar pressures may be determined during exercise without encountering the difficulties inherent in the classical direct methods. (Authors' summary).—*On the Determination of the Physiologically Effective Pressures of Oxygen and Carbon Dioxide in Alveolar Air*, R. L. Riley, J. L. Lilienthal, Jr., D. D. Procmel & R. E. Franke, *Am. J. Physiol.*, September, 1946, 147: 191.—(G. C. Leiner)

Alveolar and Arterial Oxygen Pressure.—By means of new techniques, measurements have been made in man of the oxygen pressure gradient existing between the alveolar air and the peripheral arterial blood, during rest and exercise, at sea level and at simulated altitude. At rest the gradient averaged 9 mm. Hg and during exercise 16.5 mm. Hg; the development of anoxia produced no significant changes in the size of the gradients. A method is presented for differentiating the total alveolar arterial oxygen pressure gradient into its two main components: membrane resistance and venous admixture. A theoretical analysis of the experimental data indicates that when the level of oxygenation was high (sea level) the observed pressure gradient resulted for the most part from the admixture of venous blood entering from poorly ventilated alveoli, the bronchial circulation, the Thebesian and anterior cardiac veins and perhaps other sources. By contrast, a low level oxygenation (anoxic anoxia) the gradient resulted largely from the pressure head which must develop across the pulmonary membrane to effect the transfer of the required volume of oxygen. Exercise, by exerting a physiological stress on the mechanisms serving the transfer of oxygen from alveolar air to arterial blood, evokes an integrated series of respiratory and cardiovascular adaptations, one of which is the increase of the alveolar-arterial oxygen pressure gradient. The diffusion constant of the lung, calculated from the experimental observations, averaged 21 at rest (range 12 to 36) and increased during exercise to an

average of 62 (range 50 to 76). (Authors' summary.)—*An Experimental Analysis in Man of the Oxygen Pressure Gradient from Alveolar Air to Arterial Blood during Rest and Exercise at Sea Level and at Altitude*, J. L. Lilienthal, Jr., R. L. Riley, D. D. Procmel & R. E. Franke, *Am. J. Physiol.*, September, 1946, 147: 199.—(G. C. Leiner)

Hemodynamics in Phosgene Poisoning.—Circulatory measurements were made on anesthetized and unanesthetized dogs before and after exposure to phosgene. There was a decrease of the pulse rate and of the arterial pressure. The venous pressure remained unchanged. The blood volume decreased. There was a prolonged pulmonary circulation time, an increased arterial-venous oxygen difference and hemoconcentration. Spasms of vessels were seen. Death is due primarily to an interference with oxygen uptake because of pulmonary edema. If the acute stage of pulmonary edema with its attendant anoxic anoxia is survived, circulatory failure may become a more important factor in the ultimate outcome. Venesection is not indicated in phosgene poisoning.—*Hemodynamics in Pulmonary Irritant Poisoning*, H. M. Patt, J. M. Tobias, M. N. Swift, S. Postel & R. W. Gerard, *Am. J. Physiol.*, October, 1946, 147: 329.—(G. C. Leiner)

Respiration in Cardiac Dyspnea.—Records of chest movements during breathing were made with a Marey pneumograph in normal subjects, in patients with cardiac dyspnea and in patients with bronchial asthma. The relation of expiratory to inspiratory phase in 5 normal persons at rest varied from 1.30:1 to 1.96:1, the average being 1.61:1. After exercise the average fell to 1.39:1. In 11 patients with heart disease at rest the ratio was between 1.52:1 and 2.90:1, with an average of 2.17:1. After exercise the ratio remained unchanged or decreased only slightly. In 2 patients with bronchial asthma the ratio was at rest 2.14 in average; after exercise it was 1.81. The intravenous administration of aminophyllin produced in cardiac

and in bronchial asthma a marked relative shortening of the expiratory phase. The vital capacity increased in patients with cardiac and in patients with bronchial asthma after injection of aminophyllin; in a normal subject there was only an insignificant increase. From these observations it is concluded that bronchospasm is present in both groups of patients.—*Abnormalities of the Respiratory Pattern in Patients with Cardiac Dyspnea*, H. E. Heyer, *Am. Heart J.*, October, 1946, 32: 457.—(G. C. Leiner)

Pulmonary Permeability.—Pulmonary permeability was studied by injecting ethyl alcohol intravenously and determining the output in the expired air. A detailed description of the method and its causes of error is given. Clinical experiments did not permit to establish any correlation between the condition of the lung and the elimination of alcohol. Disturbances of pulmonary permeability are not considered to be clinically significant. What counts in pulmonary permeability, is not so much the total surface of the lung but the relation between surface and alveolar volume. Most lung diseases did not modify this relation with the exception of generalized emphysema in which a slight reduction of the factor was found.—*Est-il possible de faire l'examen fonctionnel du poumon par des tests d'élimination des substances volatiles? Y a-t-il des troubles cliniques de la perméabilité pulmonaire?*, R. Monod & M. Cara, *Le Poumon*, September-October, 1945, 1: 257.—(V. Leites)

Phrenic Nerve Response to Lung Inflation.—The influence of changes in lung volume on the discharge of impulses by single phrenic motor neurones was investigated in cats anesthetized with Dial or decerebrated under ether. Inflation of the lungs inhibits the phrenic discharge for a length of time that increases with the volume of inflation. Large inflations, in addition to this well-known inhibition of inspiration, have an excitant action which is revealed by a brief burst of motor impulses as the lungs expand. This

excitant action is of short duration and has a threshold which is relatively independent of the rate of distention. The inspiration-exciting reflex is independent of vascular pressure receptors since it is not reduced during occlusion of the pulmonary artery. Both the inhibition and excitation of inspiration by lung inflation are eliminated by cutting both vagus nerves. It is suggested that these reflexes are due to impulses from two distinct sets of pulmonary receptors of different thresholds and different rates of adaptation. Increased activity of phrenic motor neurones is caused by artificial distention of the lungs only when the lungs are inflated to a volume which exceeds that reached in eupneic respiration. Following a suddenly induced pneumothorax the next inspiration is very much prolonged, but the frequency of discharge follows exactly the same time course as in normal inspiration up to the time when the normal discharge is abruptly curtailed. Inspiration is thus uninfluenced by impulses from pulmonary stretch receptors until its termination is suddenly brought about by the inspiration-inhibiting reflex. The inspiration-exciting reflex initiated by superinflation of the lungs is inactive in normal eupneic breathing, but may serve to increase the depth of any unusually deep inspiration. (Authors' summary.)—*Excitation and Inhibition of Phrenic Motoneurons by Inflation of the Lungs*, M. G. Larrabee & G. C. Knowlton, *Am. J. Physiol.*, September, 1946, 147: 90.—(G. C. Leiner)

Pulmonary Calcifications.—It was recently reported that pulmonary calcification is more frequently associated with sensitivity to histoplasmin than to tuberculin or coccidioidin in the central eastern portion of the United States. In the past few years pulmonary calcification in tuberculin-negative persons has been demonstrated in many of the central eastern states and other agents than the tubercle bacillus have been considered as the possible causative factor. Aronson presented evidence favoring coccidioidomycosis among the Indians in the Southwest. Smith has

shown that the area of prevalence of tuberculin negative pulmonary calcification corresponds with the endemic area of histoplasmosis. The study presented is based on data by Palmer and additional material collected with the help of the National Tuberculosis Association, the United States Public Health Service and a large number of schools of nursing. There is a wide variation of pulmonary calcification geographically but the positive reaction to histoplasmin closely parallels the incidence of calcification but no such parallel with positive tuberculin reactions was apparent in this material. Four times as many nurses showed calcification in Kansas City as in Philadelphia and over four times as many were sensitive to histoplasmin. All but 38 of 532 tuberculin-negative persons were histoplasmin positive. There are no generally accepted criteria for the recognition of pulmonary calcification. A total of 6,199 student nurses were X-rayed and tested with tuberculin and histoplasmin. Pulmonary calcification was found in 698, 57 of whom were tuberculin-positive, 109 tuberculin- and histoplasmin-positive. Little association could be found between questionable calcification and sensitivity to either antigen. An attempt was made to differentiate between calcification presumably due to tuberculosis and that presumably due to histoplasmosis or an immunologically similar disease. The total number of calcific deposits did not seem to differ in the two groups and no striking or characteristic feature of the individual lesions has been noted which would be of value in determining the etiological factor. It is possible that histoplasmosis is responsible for most instances of scattered multiple bilateral calcifications. Massive calcification in the hilar zones has frequently been considered pathognomonic of healed tuberculosis, but from these studies it is evident that such areas need not represent previous tuberculous infection. It is likely that sensitivity to histoplasmin is an indication of previous infection with the fungus *Histoplasma capsulatum* or an immunologically related organism, and that infection with these organisms is

not necessarily serious or fatal but is widespread in subclinical form. Since it is impossible to distinguish between the calcifications resulting from the two infections it may be inferred that the roentgenographic appearance of the benign form of histoplasmosis may resemble tuberculosis during the active phase. The tuberculin reaction and finding of tubercle bacilli are, therefore, essential in the diagnosis of pulmonary tuberculosis.—*Pulmonary Calcification: Roentgenographic Observations in Relation to Histoplasmin and Tuberculin Reactions*, H. B. Zwerling & C. E. Palmer, *Radiology*, July, 1946, 47: 59.—(G. F. Mitchell)

Pulmonary Calcifications and Age.—Intrathoracic calcifications following tuberculous infection were studied in 1,457 American Indian children who were the control group in previously reported studies on BCG vaccination. In this group, 198 developed tuberculosis; calcifications subsequently occurred in 49 of these children. Calcified foci were seen most frequently during the second and third years following the first lesion. In the youngest age group, calcification developed in 76.5 per cent of tuberculosis cases. The rate declined in older children, and was found in only 2.4 per cent of tuberculosis cases in which the disease started between the ages of 15 and 19. It is concluded that the frequency with which calcification develops in pulmonary tuberculosis varies directly with the age at which the tuberculous lesions begin.—*Variation with Age in the Frequency of Tuberculous Pulmonary Calcification*, R. H. High & H. B. Zwerling, *Pub. Health Rep.*, December 6, 1946, 61: 1769.—(M. Pinner)

Pulmonary Calcifications.—A total of 113 cases of disseminated pulmonary calcifications were studied. Of these, 64 cases were derived from an X-ray survey of 15,980 school children in Kansas City. An additional 49 cases came from other sources. Of the total 113 cases, 69, or 61.1 per cent, had multiple bilateral calcifications, while 44 had

calcifications of the milary type. Calcifications in the hilar lymph nodes were seen in 73.5 per cent of the former type and in 50.0 per cent of the latter type. The prevalence of calcifications increased with age, being zero in children under 4 years and increasing to 10 per thousand in the age group of 16 to 18. They were about four times as frequent in whites as in Negroes. No persons with calcifications reacted to tuberculin only; 93.5 per cent of persons with disseminated calcifications reacted to histoplasmin alone. Two cases reacted both to tuberculin and to histoplasmin, and 2 reacted to neither substance. In the whole group of 113 cases, 96.3 per cent reacted to histoplasmin, and only 4 did not react to it. None of the group reacted only to tuberculin. This study provides further circumstantial evidence in support of the working hypothesis that, at least in some parts of the U.S.A., disseminated calcifications are caused by whatever agent produces sensitivity to histoplasmin.—*Disseminated Pulmonary Calcification*, R. H. High, H. B. Zwerling & M. L. Furcolow, *Pub. Health Rep.*, January 8, 1947, 62: 20.—(M. Pinner)

Calcifications in Spleen.—As incidental findings in an X-ray survey in Kansas City, 20 cases of splenic calcifications were found. It is in this geographical area of the U.S.A. that about 40 per cent of white school children (and a somewhat lower percentage of Negro school children) react to histoplasmin. Among children with pulmonary calcifications, about 80 per cent react to histoplasmin, and it was found the 78.6 per cent of children with splenic calcifications reacted to histoplasmin. The close similarity in the prevalence of histoplasmin reactors among children with pulmonary and with splenic calcifications suggests that extrapulmonary calcifications are probably caused by the same agent that causes pulmonary calcifications, and that produces skin sensitivity to histoplasmin. Splenic calcifications indicate that the causative agent may be disseminated hematogenously, and apparently without

causing obvious clinical disease. It is not likely that tuberculosis is the most frequent cause of splenic calcifications in this geographical region.—*Calcifications in the Spleen, R. H. High, Pub. Health Rep., December 6, 1946, 61: 1782.*—(M. Pinner)

Upper Respiratory Infections.—The factors involved in the control of upper respiratory infections, mostly caused by hemolytic streptococci, are discussed. For climatic reasons, training camps should be situated in the southern part of the country. Overcrowding must be avoided: minimum living space requirements, established usually according to the standards of the Medical Department, are at times far from ideal in regard to epidemic disease control. In some epidemic areas, even these minimal standards have not been adhered to. The introduction, at frequent intervals, of new and usually susceptible recruits into battalions where streptococcal infection is prevalent, is an ideal condition for building up and maintaining epidemics. Instead, recruits should be grouped as fast as possible into self-contained battalions into which no new recruits should be transferred during the training period. After a battalion has been moved out, the vacated living quarters should be thoroughly cleaned, aired and disinfected. Present barracks designs foster the spread of epidemics. The incidence of streptococcal infections is more closely related to the number of men housed under one roof than to the space allotted per man. A maximum of 4 men per room is an ideal practical arrangement. Mere partitioning of barracks into cubicles, with a common aisle between them, is ineffective. Changes in basic design can be considered for future construction only. Multitudes of organisms, including hemolytic streptococci, are harbored in floor dust and bedding lint and become air-borne whenever the dust is disturbed or the bed clothes are shaken. Elimination of dry sweeping and oiling of bedding and floor, with the exception of rough concrete and linoleum, are highly recommended. Oil on bed clothes is hardly

noticeable; on floors, it soaks in within a few hours; it immobilizes dust and bacteria but has no bactericidal effect unless a germicide has been added. Ultraviolet irradiation of air and surfaces has been effective in killing bacteria but is expensive, it would be extremely useful in communicable disease wards of hospitals. Ultraviolet light plus oiling reduces air-borne organisms by as much as 80 per cent, thus diminishing cross-infection. Propylene and triethylene glycol used in aerosols condense on, and kill bacteria in the air, but do not kill organisms present on surfaces. Their wide-spread use has not yet proved practicable, but they may be found useful in selected places. Patients with upper respiratory infections should be segregated in hospital wards limited to the exclusive care of such cases. Ideally, these wards should offer single rooms and be managed as contagious disease wards, with no free communication allowed between patients and the medical and nursing staff employing the proper isolation technique. If this should not be possible, each bed should be placed in an improvised cubicle made of sheets or built-in partitions. After recovery the patient should be moved to a ward of similar design, reserved for patients convalescing from upper respiratory infections. If, at this stage, cultures from nose and throat are positive for hemolytic streptococci, penicillin should be administered. After two consecutive cultures have been negative, the patient can be returned to his company. This process should not require more than fourteen days and will save many man-days. In order to correct some of the factors which at present operate to produce cross-infections and new cases, the following measures are recommended: (1) segregation, in the waiting rooms, of patients with upper respiratory infections; (2) assigning of staggered sick-call hours for the various activities or units of the command; (3) proper sterilization of all items of common use. Mass prophylaxis with sulfonamides is not satisfactory; infections caused by drug resistant strains become epidemic. Other agents now available are not encourag-

ing. The results of active immunization with killed whole organisms of prevalent types, as well as type-specific antigenic components of the cells do not justify the use of this method for mass protection. Passive immunization with gamma globulin has, on the whole, been disappointing.—*Control of Upper Respiratory Diseases, (not signed), Bull. U. S. Army Med. Dept., December, 1946, 6: 675.—(O. Pinner)*

Upper Respiratory Infections.—In 13 patients who were hospitalized because of upper respiratory infection electrocardiographic changes were observed. Group A beta-hemolytic streptococci were present in the nasopharyngeal cultures of 5 of these patients; in one case a Group B and in one a Group G beta-hemolytic streptococcus was found. In 6 cases repeated cultures showed only the usual nasopharyngeal organisms. The most frequent electrocardiographic changes were T-wave inversions and depressions. With the exception of one, none of the patients was acutely ill. None of these patients had cardiac signs or symptoms when the electrocardiographic changes were observed. Only one patient developed clinical manifestations suggesting rheumatic fever. All patients recovered. A nonspecific toxic etiology is assumed. Sulfonamide administration may be an additive factor.—*Electrocardiographic Changes Occurring during Upper Respiratory Infections, D. Young, Am. Heart J., September, 1946, 32: 383.—(G. C. Leiner)*

Cure of Early Bronchiectasis by Pneumothorax.—This report from the Mt. Sinai Hospital, New York, based on 6 cases, gives an enthusiastic recommendation for the treatment of bronchiectasis by pneumothorax in all cases where the usual measures fail (chemotherapy, bronchoscopic aspirations, partial drainage, etc.) and where absence of adhesions permit a selective collapse of the diseased lobe. The collapse need be maintained for only six months, as complete recovery was attained in this period, and the reexpanded lobes have remained cured over periods ranging from seven to thirteen years. Favorable results

with pneumothorax therapy in chronic cases is apparently possible if a selective collapse can be obtained; the failures may be treated by radical surgical measures. Pneumothorax therapy, if employed judiciously, has no mortality, no morbidity and no serious complications. In the pathogenesis of bronchiectasis, bronchial dilatation is caused by the weakening of the muscular and elastic tissues by infection. This dilatation is augmented by cough, by bronchial obstruction, by the pull on the injured bronchi exerted during inspiration by the expanding thorax transmitted through atelectatic lung instead of through elastic parenchyma; and by the pull of the more negative intrapleural pressure which is found in the presence of atelectasis or fibrosis. With these factors in mind the objectives in treatment of bronchiectasis are: (1) to diminish the trauma of respiration by decreasing its force; (2) to minimize the trauma of cough; (3) to counteract the increased pull on the diseased bronchi because of lowered intrapleural pressures; (4) to eliminate the infection in lung and bronchi. Case reports show that pneumothorax can accomplish these objectives, since cough promptly decreased and then disappeared within one to four weeks; infection subsided promptly and permanently. In case reports it is also shown that suppurative bronchopneumonia can result in the rapid development of sacular bronchiectasis, and that pneumothorax therapy is not only an effective measure in preventing the development of bronchiectasis, but also in its treatment. In these cases, pneumothorax was tried only after two months of treatment by other measures: postural drainage, repeated bronchoscopic aspirations, generous use of expectorants (iodides), frequent inhalations of 5 per cent carbon dioxide in oxygen, inhalations of steam as well as chemotherapy. When these measures failed, pneumothorax was tried and brought about cures. These cases were treated in the prepenicillin period, and the best way to use this drug, whether by inhalation spray, by catheter instillation, by injection or whether by all methods simultaneously, has not yet been determined.—*Pneumothorax Therapy for*

Early Bronchiectasis, H. Hennell, *J. Thoracic Surg.*, August, 1946, 15: 239.—(W. M. G. Jones)

Flagellate in Bronchiectasis.—It is generally recognized that only one flagellate normally lives in the mouth of man—genus *Trichomonas* Donne. A patient is reported in whose sputum many flagellates were discovered. He was admitted to hospital with diagnosis of malaria. Despite vigorous antimalarial therapy pyrexia continued. He started to expectorate a considerable amount of foul smelling sputum. A lung abscess was diagnosed two weeks after admission and under sulphonamide therapy pyrexia declined, but quantity of sputum and respiratory distress were unchanged. Original examination of the sputum revealed numerous flagellates and spirochaetes in addition to the customary fauna. Further examinations, with careful attention to avoidance of contamination, revealed the same picture. Gradually they decreased and finally no flagellates were found. Patient died three weeks after admission. Necropsy showed bilateral pulmonary fibrosis, with numerous irregularly shaped cavities filled with foul smelling gelatinous secretion. Histological examination confirmed the diagnosis of longstanding cylindrical bronchiectasis. No flagellates were noted in cavity secretions post-mortem. The flagellate recovered from the sputum was pear-shaped, 10 to 15 μ in length, with two equal flagella at the narrow end. It is considered that this was either *Trichomonas tenax* or the flagellate stage of *Dimastigamoeba gruberi*, which had entered the lungs via the mouth and had there found in the mucopurulent material of the bronchiectatic cavities an ideal medium on which it had rapidly multiplied. The authors state that there is little reason to doubt that these flagellates are nothing more than commensals living saprophytically on the decaying contents in the bronchiectatic cavity and have apparently no pathological significance.—*Occurrence of a Flagellate in the Sputum of a Case of Bronchiectasis*, G. O. Lehmann & J. T. Prendiville, *Brit.*

M. J., February 2, 1946, 1: 158.—(D. H. Cohen)

Bronchiectasis and Atelectasis.—Four cases of atelectasis with bronchiectasis are described. In all 4 cases, reaeration and reexpansion of the collapsed portion of the lung occurred. In 3, there was retrogression of the bronchiectasis; in the other case, it persisted.—*Bronchiectasis and Atelectasis: Temporary and Permanent Changes*, F. P. L. Lander, *Thorax*, September, 1946, 1: 198.—(A. G. Cohen)

Atelectatic Bronchiectasis.—Shadows representing the right middle lobe in the conventional postero-anterior view are often difficult to interpret. Lateral views help but sometimes the shadow of the atelectatic lobe is hardly denser than that of the normal lung. In fact, this is often also true in postero-anterior views. It is believed that the lordotic position brings the interlobar septum more or less in the plane of the rays. Fourteen cases of atelectatic bronchiectasis of the right middle lobe were seen in an eighteen-month period. In most cases, with or without purulent sputum, had been present since an early age. Slight variable physical signs referable to the middle lobe were found in less than 50 per cent of cases. Roentgenograms in the conventional views were normal in many cases. Abnormal findings included increased striation at the right base, hazy opacity in the region of the lower pole of the right hilum extending a little way into the lung field and enlargement of the lower pole of the root of the right lung with or without downward retraction. The lordotic view showed a triangular shadow with its base on the right cardiac border below the hilum and its apex somewhere in the middle of the lower lung field. The upper and lower margins were sharp. This area was denser than the surrounding lung field. The shadow was seldom homogeneous. Bronchograms taken in the lordotic position served to dissociate the shadows of the middle lobe bronchi from those of the lower lobe. Lipiodol was seen to enter the involved area and bronchiectases were found.—*Atelectatic Bronchiectasis of the Right*

Middle Lobe, A. T. Doig, *Tubercle*, November, 1946, 27: 178.—(A. G. Cohen)

Hemoptysis and Bronchoscopy.—Among 332 bronchoscopies performed for various reasons, 80 (24 per cent) were indicated by a previous hemoptysis. Hemorrhagic tracheobronchitis was found in 38 cases, 19 of these had active or arrested pulmonary tuberculosis. Bronchoscopy revealed bronchogenic carcinoma in 12.5 per cent of the cases, benign bronchial tumors in 5 per cent, bronchiectasis in 15 per cent, bronchial stenosis in 7.5 per cent. There was no demonstrable bronchial abnormality in 7.5 per cent of cases. It is concluded that in 90 per cent of the cases with hemoptysis bronchoscopy permitted to determine the tracheobronchial origin and the specific cause of the bleeding.—*Hemoptysie et endoscopie bronchique, une statistique de 80 cas*, P. Mounier-Kuhn, C. Ollagnier & A. Persillos, *Le Poumon*, July-August, 1946, 2: 18.—(V. Leites)

Aerosol in Asthma.—Eighty-four patients with acute or chronic asthmatic dyspnea were treated with inhalation of nebulized bronchodilator drugs, chiefly 0.2 per cent Alendrine (isopropyl adrenaline) which is reported to have ten times the bronchodilator power of adrenalin, with or without 0.5 to 1.0 per cent Adrianol (neosynephrin). The results are classified according to the age, sex, duration of treatment, type of dyspnea and intensity of the symptoms, and by dominant etiological factor. All 84 patients are stated to have experienced some relief, most of them markedly so.—*La thérapeutique pro longue des dyspnoes asthmatiformes par les aerosols medicamenteux pneumodilatateurs*, R. Charlier, *Rev. belge sc. méd.*, February, 1946, 16: 42.—(E. Bogen)

Treatment of Pulmonary Actinomycosis.—This report deals with 19 cases from Barnes Hospital since 1925. (Total number in all

reports, therefore, 52). Of these 19 cases, all had proved laboratory diagnosis, but the author believes many cases may have been missed due to the difficulty in finding the organism, which in some cases took as long as two to three years. Eight of the 19 cases have died as a result of the infection or its complications; 6 of these died by generalization of the disease. In 5 patients the disease first made its appearance in the intestinal tract, and these all did poorly. Only 6 professed any association with cattle. Detailed reports of the cases that recovered are given. Surgical drainage or resection of diseased tissue was performed in all patients, supplemented by penicillin or sulfonamides, or small doses of X-ray irradiation in certain instances. Other adjuvants used formerly were thymol and potassium iodide in addition to surgery. The author was struck by the remarkable benefits of penicillin to control the most severe symptoms, and believes this drug will supercede all others, to supplement the surgical treatment. About 25 per cent of all infections are present in lung and chest wall; 60 per cent in the jaw and cervical regions. The pulmonary picture presented by these cases is that of a chronic pneumonitis accompanied by fever, cough and especially chest pain. The infection extends over many months. Lung abscesses tend to be small and multiple. The disease may extend in any direction, peripherally involving pleura, periosteum and ribs. Chest wall sinuses may enter mediastinum or spinal canal. Entrance into blood stream proves rapidly fatal. Diagnosis is best made from tissue section. Material directly aspirated from an abscess or obtained through a bronchoscope is more satisfactory than discharge from a sinus tract. The fungi can be cultured and this should always be done in suspected cases.—*Treatment of Pulmonary Actinomycosis with a Report of Seven Arrested Cases*, J. K. Poppe, J. Thoracic Surg., April, 1946, 15: 118.—(W. M. G. Jones)

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TUBERCULOSIS IN EUROPE AFTER THE SECOND WORLD WAR¹

JOHANNES HOLM²

Experience has shown that an increase in tuberculosis follows every war. This was indeed the case after the last World War, and the increase in tuberculosis in Europe to-day is perhaps greater than after any war in the past. It has often been considered natural that this should occur, but only insufficient explanation of the increase has been advanced. Now that we know so much more about tuberculosis than in the old days—now that we have, in particular, a better understanding of its epidemiology—we should be in a good position to seek out the cause of the present increase in the countries of Europe.

What are the causes of this increase in tuberculosis? Without doubt, the most important cause is the greater opportunity for the spread of tubercle bacilli during and since the war. The whole antituberculosis program, which was really quite highly developed in many European countries, became completely disorganized and, with few exceptions, patients with infectious pulmonary tuberculosis were neither isolated nor given medical care.

Early in the war tuberculosis patients in Germany were forced into work. Manpower was needed, and it was therefore proclaimed that no damage to the health of the patient would result from his working. Not even infectious patients were excluded from the labor force. As a consequence, many patients were seriously affected, and the spread of tuberculosis increased considerably in the places of employment. Then again, sanatoria were taken over for barracks in most of the countries occupied by the Germans. It was necessary to evacuate the patients, and they were sent home to live with their families, where the spread of infection was uncontrolled. At the same time, all organized dispensary work stopped.

In Germany and in many other European countries, two things happened that markedly increased the spread of the disease. Air raids damaged a high proportion of the dwellings, especially in the large cities and towns, and this automatically caused a crowding of the population into the remaining buildings. Because of the continual air raids, the population was forced to spend much time in air-raid shelters or bunkers, which were extremely overcrowded; and here, of course, the best opportunities prevailed for the spread of every kind of disease, including tuberculosis.

Even now, many of the increased possibilities for spreading the disease still exist. In many of the towns, and especially in the large cities, houses are damaged to such a degree that living accommodation is one-fifth of what it was before the war. And yet, practically the same number of people are living in these cities, which means, of course, terribly overcrowded conditions. In many places

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each family has only one room, and in certain areas—especially in Germany—the population has grown because of the influx of refugees. For instance, many millions of refugees still live in Western Germany, having left their homes in Eastern Germany as the Russian army swept westward. Moreover, since the war, great emigrations have taken place from certain areas, which naturally has resulted in enormous additions to the normal population of other areas. In none of these movements of population have measures been taken for tuberculosis control, and thus patients with infectious tuberculosis have been absorbed into the normal population. No wonder that, both during and after the war, greater possibilities than ever before existed for spreading tubercle bacilli.

Even in a normal population, these conditions would be serious and, in populations with lowered resistance, the problem is acute. There are several reasons for this lowered resistance. Perhaps the most important is malnutrition. In many areas of Europe the population has lived on the border of starvation. The malnutrition in Europe is so well known that it is unnecessary to go into much detail, but some factors should be mentioned which have special significance in lowering the resistance to tuberculosis.

Investigations in recent years have shown not only that the number of calories plays a rôle in resistance to the disease, but that certain elements in the diet have special importance, such as animal proteins, certain vitamins (especially vitamin C), and perhaps calcium. As an example of how insufficient the diet has been, I shall mention conditions in Vienna, where the American Forces have made a special analysis of the nutrition problem. In the official report of the American Forces in Vienna, 1946, it is stated that the average consumption of calories per person was less than 1,500 per day, and that the food contained very little animal protein and, for six months, almost no trace of vitamin C. Also, the amount of calcium in the food was less than one-third of what is considered the minimum for normal nutrition. For two years, however, the normal daily ration for the whole of Central Europe has been less than 1,500 calories per person, which is only half of what a normal Dane consumes.

On the whole, nutrition is worse in the large towns, and especially poor in the large cities. In the country, and to some extent in the small towns, the population has a chance of supplementing the ration. But in large cities, such as Vienna and Berlin, which are surrounded by Russian territory that the people are forbidden to enter, there is almost no possibility of obtaining food in addition to the normal ration.

The low standard of everyday hygiene must be mentioned as another factor in the lowered resistance to tuberculosis. In many countries the general hygiene has been set back a hundred years by the war. Facilities for hygiene simply do not exist. In Germany, for instance, soap has the highest price, next to butter, on the black market! Dr. Redeker, one of the leading tuberculosis specialists in Germany, informed me that he considered the spread of tuberculosis to be largely aggravated by the lowered hygienic standards. He stated that in Germany the men ceased to wash themselves a year ago, but that the women are still fighting desperately to keep themselves and their children clean.

As a final factor responsible for the lowered resistance, the psychic pressure under which the population has lived, and is still living, must be mentioned. We must remember that almost everyone throughout a great part of Europe has lost one or more near relations, and that many are living with no knowledge of their families. They have no future to look forward to, and hence their apathy is understandable. This, I am sure, plays a not inconsiderable rôle, even in the physical resistance against disease.

Now, what is the present tuberculosis problem in the European countries? How wide-spread is the disease in Europe to-day, and how great is the increase caused by the war?

It must be stressed at once that there is a vast difference in conditions among the various countries of Europe. It is a great pleasure for me to be able to state that there has been no definite increase in tuberculosis in the Scandinavian countries either during the war or after it. In Sweden an increase in tuberculosis perhaps could not be expected; but Denmark and Norway were occupied by German troops, and especially in Norway conditions were appalling in the last three years of the war, particularly as regards nutrition. Nevertheless, there was no increase in tuberculosis. This was probably because the highly developed tuberculosis program in Norway was functioning even under the most terrible conditions, and perhaps it is necessary to mention that Calmette vaccination was used more in Norway during the last years of the war than ever before.

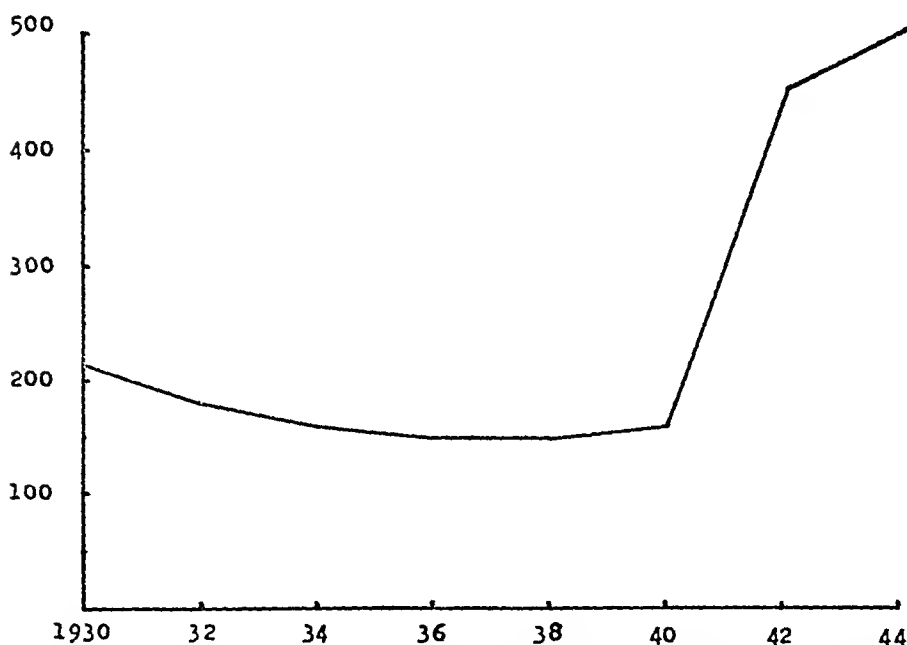
It is very difficult, for several reasons, to obtain reliable statistics concerning tuberculosis in most of the European countries. It must be remembered that in most countries there is still no really well organized tuberculosis program, and that in only a few does a system for notification of tuberculosis function. Even in the countries where such a system exists, the figures obtained are so unreliable that they cannot be compared with pre-war figures. One of the reasons for these conditions is the great shortage of physicians in most countries. In Poland, for instance, almost half the physicians were killed in the war. Again, because of the shortage of physicians, even death certificates are made out, to a large extent, by non-medical people. This, of course, results in inaccurate statistics for tuberculosis mortality, and it is quite understandable that the figures for morbidity are even less reliable.

Furthermore, it is very difficult to obtain figures for the total population on which the statistics must be based. Because of the continuous movement of population, it is almost impossible to estimate how many people have lived in a certain area. The only basis for normal population statistics is the distribution of ration cards. Even this is not too reliable, and it is impossible to obtain the age distribution by this method. It must be remembered that the age distribution in many areas differs widely from the normal. As an example of this: in Vienna in 1946, the age-group 20 to 40 years contained 73 per cent women and only 27 per cent men.

Because of the unreliability of the official statistics, I shall not try to quote figures for all the European countries, but shall only give figures from countries which I have recently visited. Even then, I shall mention statistics for only cer-

tain areas where, from discussions with tuberculosis specialists, I have gained the impression that the figures can be regarded as fairly reliable. The countries I have visited are Germany, Austria, Hungary, Czechoslovakia and Poland. I must say, however, that the increase in tuberculosis is probably worse in other countries, especially Bulgaria, Rumania and Greece.

The time at which the increase in tuberculosis began differed in various countries. In Poland, it came relatively early in the war, as could be expected. The curve for tuberculosis mortality in Warsaw shows that from 1930 to 1940 there was a decrease in tuberculosis from about 200 to about 150 per 100,000 popula-



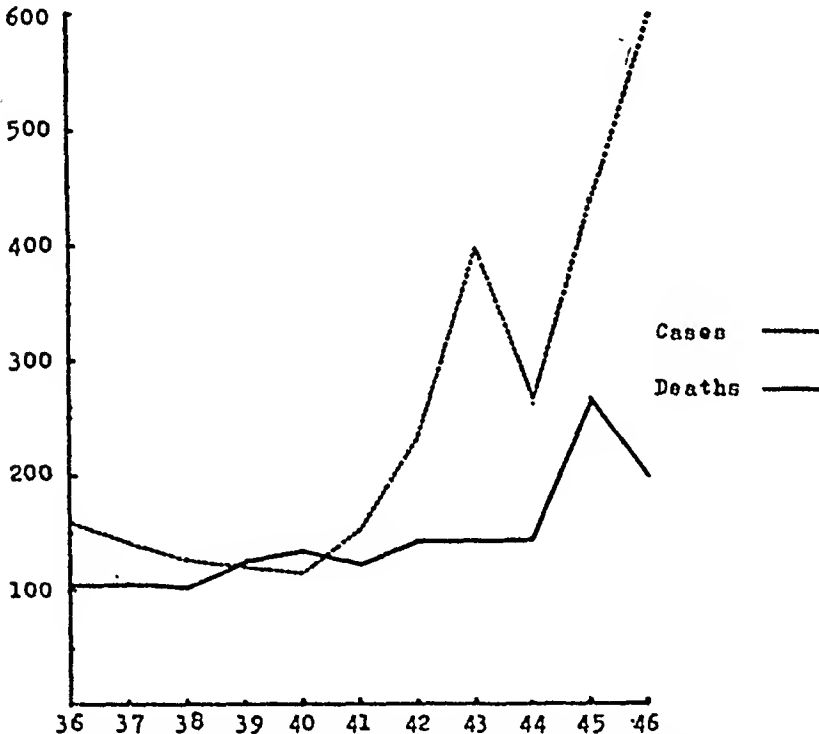
GRAPH 1. Tuberculosis death rates (per 100,000 population) Warsaw, 1930-1944. Official figures obtained from Ministry of Health, Poland.

tion. As early in the war as 1942, the mortality had increased to three times the 1940 figure, and later there was a further, not inconsiderable increase (graph 1).

In Germany and Austria, the increase did not occur until the latter years of the war. Graph 2 shows the mortality and morbidity from tuberculosis in Vienna. By 1945 the mortality had almost doubled. It was lower again the following year. There is a special explanation for the great increase in tuberculosis mortality in 1945. It was the experience of tuberculosis specialists in Vienna that the people who died of tuberculosis that year were those who had had the disease for some time. It must be remembered that conditions in Vienna, particularly in 1945, were terrible, and one would expect these conditions to have affected especially the people with tuberculosis. A high percentage of them simply died off. It will be seen from the curve that there was some increase in the morbidity

from tuberculosis as early as 1940, but the really big increase did not occur until 1944. In 1946 more than four times as many cases were reported as in the years before the war. It can be seen from graph 3, which shows the data month by month, that tuberculosis morbidity in Vienna is increasing to-day. The curve has a very steep upward trend, and it is to be expected that the mortality curve would show the same rise.

In order not to give the impression that it is only in the large cities that tuberculosis increased during and after the war, I shall quote some figures from



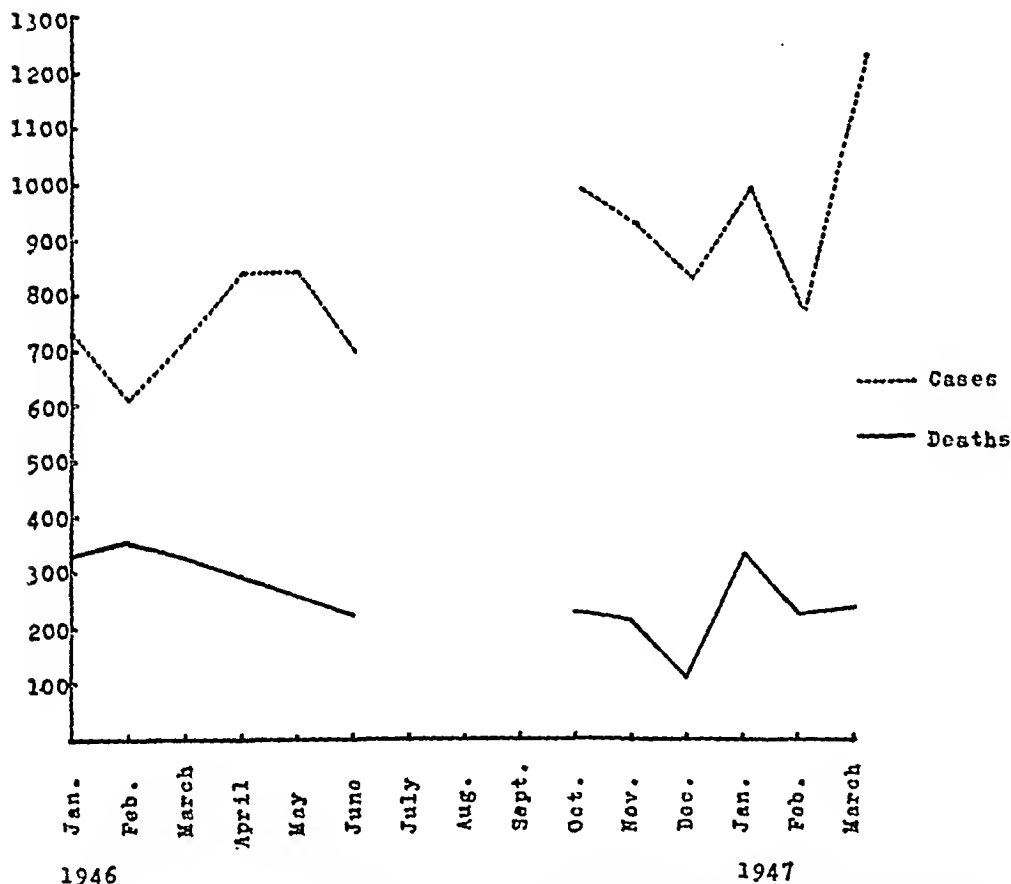
GRAPH 2. Deaths and new-reported cases of pulmonary tuberculosis in Vienna, 1936-1946 (rates per 100,000 population). Statistics obtained from *Magistratisches Amt für Statistik, Vienna* (1945-1946 figures subject to final correction).

Schleswig-Holstein in the northern part of Germany. This is a typical farming district with only a few large towns, but even there a considerable increase in both the morbidity and mortality from tuberculosis is evident (table 1). Only the morbidity and mortality figures are shown, since it has been impossible to obtain reliable statistics for the normal population and, hence, impossible to give the rates per 100,000 inhabitants. On the whole, the population was relatively stable in this area until 1945, but in that year the population almost doubled—from 1.5 to 2.7 million. Even if this is taken into consideration, the number of deaths and the new cases of tuberculosis are several times as high as they were before the war. In Schleswig-Holstein, tuberculosis is still increasing, as may be

TABLE 1

Number of new cases and deaths of tuberculosis in Schleswig-Holstein, 1939-1946

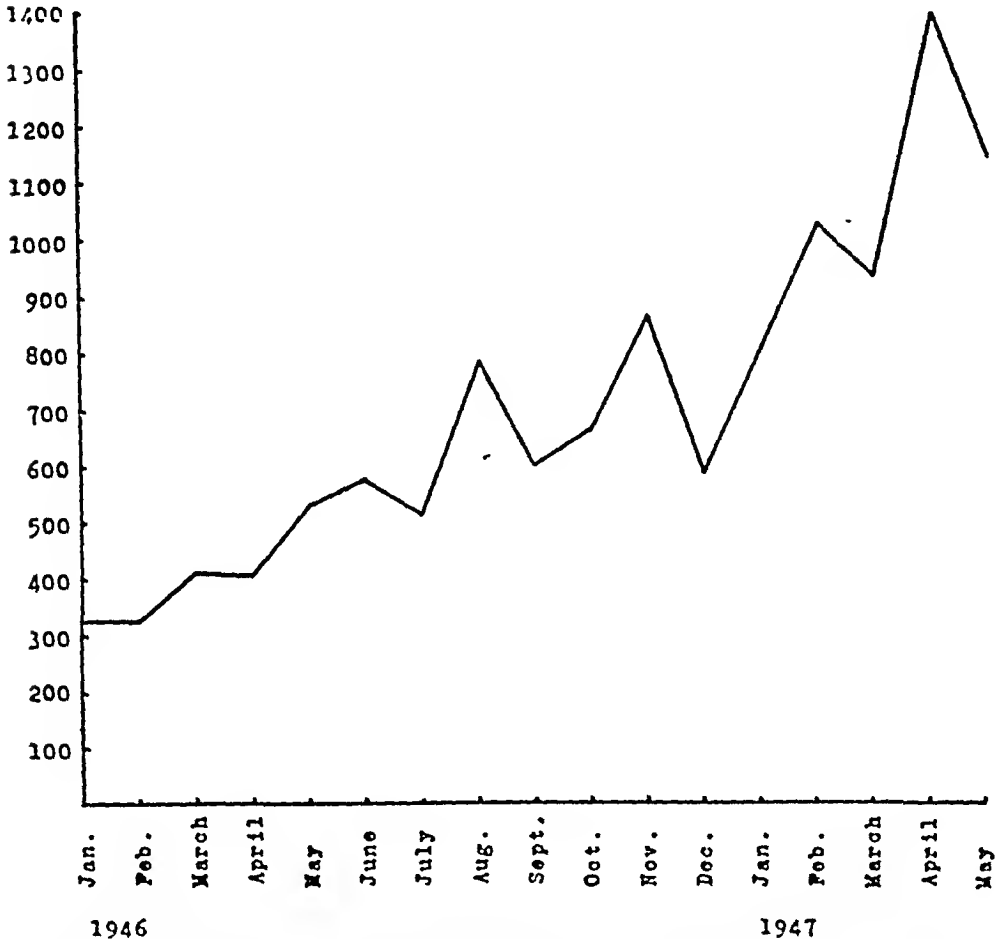
YEAR	CASES	DEATHS
1939	1,252	407
1940	1,242	449
1941	1,516	578
1942	1,818	442
1943	2,414	637
1944	3,191	721
1945	6,034	1,332
1946	6,575	2,754



GRAPH 3. Number of deaths and new-reported cases of pulmonary tuberculosis per month in Vienna, January, 1946 to March, 1947. Statistics obtained from *Magistratisches Amt für Statistik*, Vienna.

seen from graph 4, which shows the number of new cases per month since January, 1946. The curve has a distinct upward trend.

In order to arrive at a detailed explanation of the increase in tuberculosis, it would be necessary to know the age distribution of the cases. As mentioned before, however, this has been impossible to obtain. Nevertheless, it is the general impression of specialists in the various countries that the increase is especially great among children and young adults.



GRAPH 4. Number of cases of tuberculosis reported in Schleswig-Holstein, 1946-1947. Population in Schleswig-Holstein 1946 was 2,790,000.

During my study of the tuberculosis problem in the countries of Europe, the condition that made the deepest impression upon me was the vast number of cases of tuberculous meningitis among children. In some countries tuberculous meningitis among children is almost epidemic. Even the cases of pulmonary tuberculosis among children in these countries are quite different from those we usually see—at any rate in Denmark. In Vienna and Warsaw, I observed, even among small children, many cases of tuberculosis of a typical adult type, with large cavities. There has also been a tremendous increase in extrapulmonary

forms, such as tuberculosis of the bones, joints and kidneys. It has been possible to obtain some figures for Poland that show the increase in tuberculosis among children. In Poland in 1946 the tuberculosis morbidity for all persons was twice the pre-war figure, but for children, four times as many cases were reported as before the war.

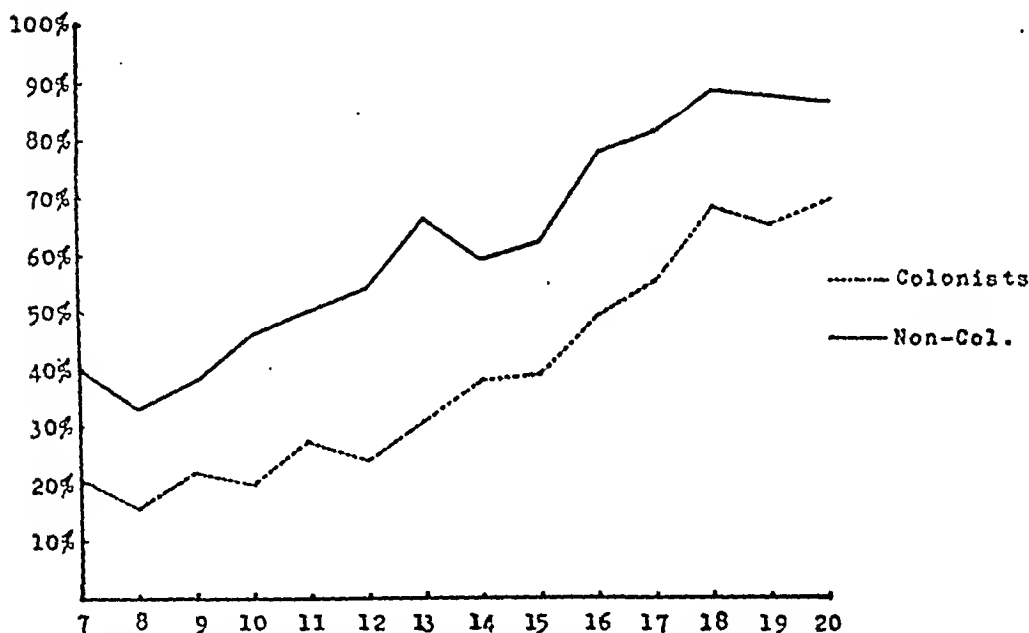
Among adults, the increase is greatest for the young, and particularly for males. From the figures on tuberculosis after the first World War, it is known that the increase was especially high among young adults, but at that time it was mainly the women who were affected. In Berlin in 1946 the mortality from tuberculosis was 302 per 100,000, as against 82 before the war—an increase of more than 350 per cent. At the same time, there were five times as many cases among men as among women, in the age-group 18 to 40 years.

The specially high increase among children and young adults points to the fact that many of the cases are primary tuberculosis. This has been ascertained from the direct experience of tuberculosis specialists in the various countries. No wonder it is so dangerous for young adults to get a primary tuberculous infection under conditions such as those which exist in many European countries to-day! In Denmark, investigations in recent years have shown that, among adults with primary tuberculous infections, 5 per cent contract a progressive tuberculosis. This demonstrates the danger of the so-called natural vaccination. These investigations were made among a population living under good nutritional and social conditions; but under present conditions in many European countries, the percentage contracting progressive disease will certainly be very much higher.

This raises the question of how many of the adults, especially the young adults, are nonreactors to tuberculin and, in particular, were nonreactors before conditions became so bad. Tuberculin tests made before and during the war, on the normal population in Germany for instance, show that the reactor percentage was relatively low in many areas. A tuberculin examination made on the recruits in the German army in 1942 shows that in the 20-year age-group only 60 per cent were reactors. In recent years examinations have shown an increase in this percentage. An examination of school children in Schleswig-Holstein in Germany, made by Doctor Hein, showed that, in 1942-1943, 38 per cent were reactors at the age of 14. An examination made in 1946 by the same doctor among exactly the same groups showed more than 50 per cent reactors at the same age.

It is of course dangerous to have so many nonreactors to tuberculin among young adults under conditions where the possibility of infection is so much increased. After the first World War, the percentage of tuberculin reactors was much higher all over Europe, and practically the whole population was tuberculin-positive at the age of 14. The tremendous increase in tuberculosis after World War II may be explained by the great number of young adults who are nonreactors to tuberculin. When a population living under post-war conditions is heavily exposed to tuberculosis, a great number of primary infections will result, not only among children but among adults as well, and this must cause many cases of primary tuberculosis.

The great movements of population which have taken place with no tuberculosis control have resulted in the people of an area with a low percentage of reactors moving to another area with a high percentage. That this has actually happened has been demonstrated by the examinations carried out by Danish doctors sent to Yugoslavia and Germany by the Danish Red Cross. In Yugoslavia a great number of people from Montenegro, which for many years has had a low incidence of tuberculosis, were sent down to Vrbas in another part of the country (graphs 5 and 6). An examination made in Vrbas showed a great difference between the reaction percentages of the stable population and the colonists. At the same time, it was found that especially among the colonists a great number



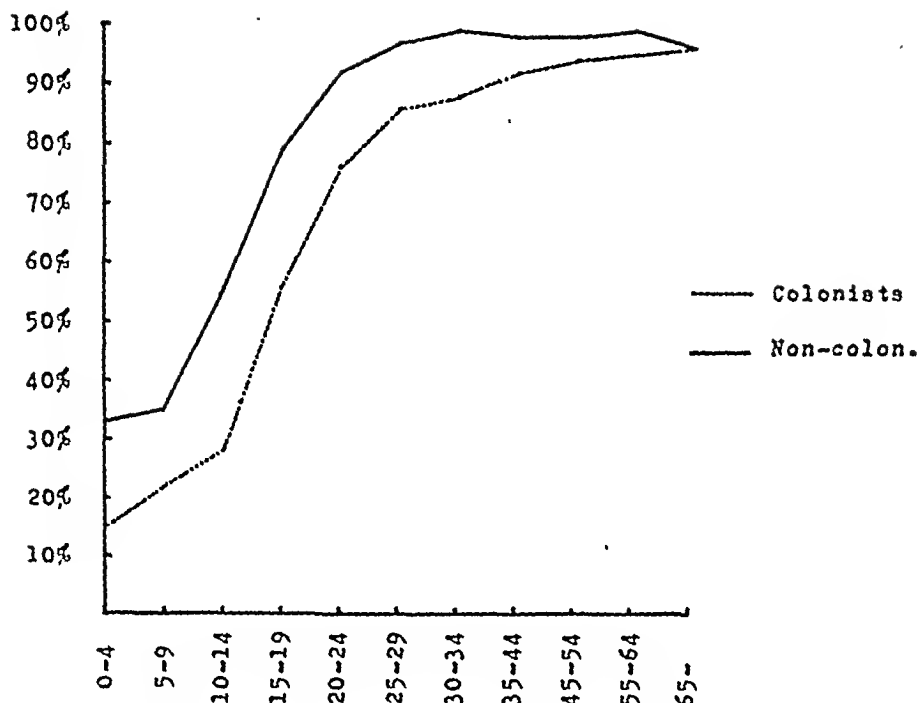
GRAPH 5. Percentage of tuberculin reactors (Mantoux test) in Vrbas, Yugoslavia, 1947, by ages. Tuberculin tests made by the Danish Red Cross.

of typical primary infections and cases of primary tuberculosis occurred, not only among children but also among adults.

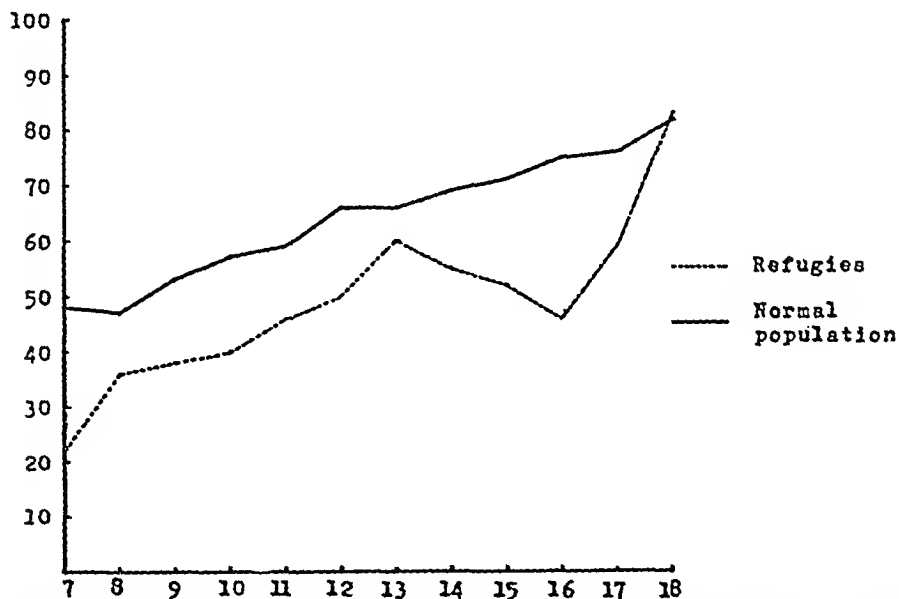
In Schleswig-Holstein, a similar difference was found between the reaction percentages of the stable population and the refugees (graph 7).

Under such conditions, it would be expected that many cases of tuberculosis would occur among the tuberculin-negative persons. We have had the same experience in Denmark, on a small scale. On the island of Bornholm, there has been a very low percentage of reactors for many years. When people from the island went to other parts of Denmark where the infection rate was higher, many of the nonreactors returned with tuberculosis.

An accurate measure of the spread of tuberculosis in a population can only be obtained through mass examination of nonselected groups. An examination car-



GRAPH 6. Percentage of tuberculin reactors (Mantoux test) in Vrbas, Yugoslavia, 1947, by age groups. Tuberculin tests made by the Danish Red Cross.



GRAPH 7. Percentage of tuberculin reactors (Mantoux test) on school-children in Schleswig-Holstein, 1947, by ages.

ried out in Warsaw by the Swedish Red Cross showed that 7 to 8 per cent of the adults had lesions in the lungs suspected of tuberculosis, and that in more than 1.5 per cent the tuberculosis was considered active. Not all of these were examined for tubercle bacilli, and without demonstration of tubercle bacilli the diagnosis is always uncertain; but from groups where examinations for tubercle bacilli were made, it was ascertained that at least 1 per cent of the total number examined discharged tubercle bacilli demonstrable in sputum.

From all this, it is evident that tuberculosis in Europe to-day has spread to an extent greater than at any other period in this century, and that the best opportunities exist for a further spread of the disease. Both the morbidity and mortality curves in many countries still show an upward trend, and this is not to be wondered at. It must be remembered that in most of these countries such tuberculosis programs as do exist are only partly functioning. In many countries there is not only a great shortage of doctors and nurses, but also a catastrophic shortage of all the equipment necessary for a modern campaign against tuberculosis, especially X-ray equipment. Furthermore, there is a tremendous shortage of institutional beds for isolation and treatment of tuberculous patients. A great percentage of sanatoria was destroyed during the war. In Poland, for instance, before the war, there were about 8,000 beds for tuberculosis patients. At the end of the war, there were only about 4,000 left, and these were in sanatoria partly destroyed and stripped of all equipment. In Poland now there are about 12,000 beds, but many more are needed. At least 60,000 beds would be needed there in order to have the bare minimum of one bed for each annual death from tuberculosis; and conditions are just the same in many other countries of Europe.

What can be done to help fight tuberculosis in Europe to-day? It must be stated at once that it is absolutely necessary to arrange for help from the outside.

What is most needed is *leadership*. It must be remembered that a great number of the leading tuberculosis specialists either died during the war or dropped out of action after the war. The reasons for this last fact vary. In Germany leading specialists in the tuberculosis campaign from 1933 to the end of the war were members of the Nazi Party, and it has therefore been difficult for many of them to take an active part in the post-war campaign. In other countries in Europe there has been a change in the political system, and many of the doctors who before the war were holding leading positions are not allowed to hold them now under the new regime. Furthermore, it must be remembered that a great part of Central Europe, including Germany and the German-occupied countries, was cut off from the rest of the world for many years, and therefore had no possibility of obtaining information on what was happening in the medical world from 1938 to the end of the war. Even now it is almost impossible for them to get medical literature from other countries. The effect of this is considerable. Within the specialty, in the last decade, there has been a great evolution called the "tuberculosis campaign," and this is new and unknown to practically all the physicians in the countries I have mentioned. At the same time, the physicians there are very eager to obtain as much information as possible from abroad. I have experienced this personally, through the lectures I have given in Europe.

A relief action is necessary; but how shall this action be organized?

In Denmark we have given this question deep consideration and have tried to arrive at a practical solution. I shall briefly mention the tuberculosis relief action organized from Denmark through the Danish Red Cross—especially because it illustrates that something can be done, and describes the program for relief to countries where the tuberculosis situation may lead to national tragedy.

This action has two aims: (1) the sending out of direct help to different countries and (2) the inviting of foreign physicians to Denmark to observe and study a modern tuberculosis program.

It is of great importance that the physicians who are going to take over the actual tuberculosis program in the different countries have an actual opportunity to see a tuberculosis program working on modern principles. Therefore, doctors from many countries in Europe have been invited to Denmark, to enable them to have an education in the different specialties within the tuberculosis program, including (1) tuberculosis dispensary work, (2) tuberculosis epidemiology, (3) bacteriology of tuberculosis and (4) therapy of tuberculosis. In connection with this action, we try to furnish the leading tuberculosis specialists with as much as possible of the tuberculosis literature published in recent years.

The aim of the direct relief action is, first of all, a large-scale Calmette vaccination, to some degree combined with diagnosis of the really infectious cases of tuberculosis. With a prevalence of tuberculosis like that in Europe to-day, it might seem hopeless to give any help. But much can be done. Tuberculosis is in an epidemic stage in many countries, and it is therefore the aim of our work to combat that epidemic along the same lines as those used for epidemics of other diseases, such as diphtheria and typhoid fever. The actual experience in the different countries, and the reliable statistics available, point to primary tuberculosis as the cause of the present great increase of the disease in Europe. Now, we know from much experience in the Scandinavian countries that these cases of primary tuberculosis can, to a large extent, be prevented by Calmette vaccination. Therefore, our first aim is to check, by Calmette vaccination, the great inflow of new cases. We have sent teams of Danish physicians and nurses to different countries in order to conduct mass tuberculin surveys and vaccination of all nonreactors to tuberculin among whole population groups. Such a team starts in a certain area and demonstrates how the mass examinations and vaccinations should be organized and carried out. At the same time, physicians from the countries concerned are taught the technique of tuberculin testing and vaccination. After the first demonstration, mixed teams are set up, consisting of Danish and local personnel; and it is our hope that later the local doctors and nurses will take over practically all the work. One team, consisting of a physician and two nurses, can tuberculin-test and vaccinate the nonreactors at a rate of 2,000 persons a day. Two Danish teams working in Warsaw have tuberculin-tested and vaccinated all the school-children in that city and have started vaccination of young adults. Altogether, there are four Danish teams, composed of five physicians and ten nurses, working in Poland. We are acting along the same

lines in the British Zones of Germany and Hungary, and are just about to start in the American Zones of Germany, Austria and Czechoslovakia.

It is our opinion that the most important part of the campaign is the vaccination—that it is of less importance to start a case-finding survey, especially one that uses a very fine diagnosis. Through X-ray examination in many countries, we would find that 1 to 2 per cent of the population had tuberculosis, but as there are no possibilities for isolation and treatment, this would be of very little help in fighting the disease. The Danish relief action, therefore, is not planned primarily as an X-ray survey; but, in order to diagnose the worst sources of infection in the population, the tuberculin test is combined with an examination of sputum for all adults with productive cough. Persons with productive cough and many tubercle bacilli in sputum must first of all be isolated in order to cut down the infection rate. Because of the shortage of food, it has been difficult in many countries to keep the infectious patients in tuberculosis sanatoria. Patients in institutions cannot obtain extra food from the black market! Therefore a number of sanatoria are provided with Danish food through the Danish Red Cross.

In addition to operations in the countries mentioned, the Danish Red Cross has worked for six months in Yugoslavia, where a tuberculosis dispensary, after Danish principles, was established as a demonstration, and the next step in the relief action will be to start such dispensaries in other countries as well. Negotiations are in progress for beginning the same type of work in Rumania, Italy and perhaps other countries.

It has been an advantage that this relief action has started from Denmark, because Denmark is a small country and permission for the work was perhaps more easily obtained than it might have been by the bigger nations. On the other hand, however, the resources of Denmark are limited, and it would therefore be most desirable to obtain help from other countries, for instance from the U. S. A.

It has been difficult in Denmark to obtain all the equipment needed for the teams already working in the various countries of Europe, and we have been most grateful to receive some help from the American Red Cross. Our greatest problem is to get such items as cars, instruments, X-ray equipment and paper.

It is not sufficient to send equipment to the different countries without teaching their tuberculosis workers how to use it correctly. I learned this from my recent visit to Prague. There I saw 15 complete sets of quite modern American apparatus for mass photofluorography, which had been sent to Czechoslovakia from the United States as a gift. Only one of these had been in use, and that for only a short time. The Czechs simply did not know how to use the apparatus or how it should be applied in a practical way in the tuberculosis campaign. This stresses the necessity for leadership and direct instruction.

In many places equipment for the tuberculosis institutions is needed. It is possible to get the buildings for sanatoria, and perhaps the beds, but bedding and other equipment cannot be obtained. Practically everywhere, there is a shortage of instruments for treatment, such as pneumothorax needles and thorascopes.

For the National Tuberculosis Association in this country, there is a great work to be undertaken in assisting voluntary agencies in Europe to get started. Send out some of your best men as observers to see the situation in Europe to-day, and you will be convinced that help is needed. Your leadership will be invaluable.

CONCLUSIONS

The tuberculosis situation in Europe to-day is serious, even very serious, but it is not hopeless!

As mentioned several times, it is necessary to bring outside help to many of the European countries. The means of providing this help exist. The main thing is to organize the help in the right way, by starting a real international coöperative effort for the fight against tuberculosis.

We used to say, "No home is safe from tuberculosis until every home is safe." Modern transportation facilitates the spreading of disease from one country to another, and therefore no nation can completely eradicate tuberculosis until it is eradicated throughout the world. By taking an active part in the international efforts to control the disease, we protect our own home and country. And thus we will not only progress in the campaign against tuberculosis, but will also contribute essentially to a better understanding among nations—an understanding badly needed in the world to-day.

CONCLUSIONES

Tuberculosis en Europa

La situación tuberculosa en Europa hoy día es grave, y podemos decir, hasta muy grave, pero no desesperada!

Como se ha dicho varias veces, es necesario llevar ayuda de afuera a muchos países de Europa. Ya existen los medios de facilitar esta ayuda. Lo principal es organizarla con acierto, iniciando una verdadera empresa cooperativa internacional para la lucha contra la tuberculosis.

Solíamos decir: "No hay hogar a salvo de la tuberculosis hasta que todos los hogares estén salvos." Los modernos medios de transporte facilitan la propagación de la enfermedad de un país a otro, por lo cual ningún país puede erradicar completamente la tuberculosis sino después que esté erradicada en todo el mundo. Participando activamente en los esfuerzos internacionales contra la dolencia, protegemos nuestros propios hogares y países. No sólo avanzaremos así en la lucha antituberculosa sino que contribuiremos fundamentalmente a una comprensión mejor entre las naciones: comprensión esta harto necesaria en el mundo hoy día.

TUBERCULOSIS IN SOUTH AMERICA¹

HÉCTOR ORREGO PUELMA²

SOCIAL AND ECONOMIC PANORAMA

To understand the tuberculosis problem in South America without an understanding of present-day socio-economic conditions and racial factors in the various countries is an impossibility. We, therefore, wish to commence by sketching briefly the salient social, economic and geographical features of the Continent.

The twenty Latin-American Republics have a total population of 130,000,000 inhabitants, spread over approximately 20 million square kilometers. Thus a population similar in number to that of the United States occupies two and a half times the latter's territory, suggesting a lower level of population density in South America than in the United States. However, due to the vast stretches of jungle, mountain, desert and other uninhabited land in South America, the population is not as thinly spread as these figures might seem to suggest. *The low population density is apparent rather than real; and it is necessary to use other and more accurate measures of population concentration, such as the number of persons per room or per bed, if we wish to obtain a true picture of population conditions as they concern tuberculosis and the possibility of spread of infection.* No detailed statistics are available, but the few inquiries that have been made indicate that there is much more crowding, that is, many more people per room and per bed in South America than in the United States. If we add to this "crowding" of people together, the low standard of living of the majority of the people, it seems reasonable to conclude that South Americans are much more exposed to contagious air-borne diseases than North Americans.

Sayé points out that in the last ten years the highest mortality rates known have been registered on the Pacific Coast of South America and that, although the demographic displacements that have taken place here are not comparable with those of Europe during the second half of the 19th Century, the tubercularization waves have been produced by population shifts to the cities and, in general, by an intensification of industrial, agricultural and commercial activities.

A person crossing the United States from San Francisco to New York, by way of Chicago, would find that both the standard of living and the mixture of races were fairly similar throughout all stages of his journey. In Latin America the same traveller would receive quite a different impression.

From the racial point of view, Latin America can be divided into three large geographical areas. The countries making up the tropical areas are inhabited by Indians, Negroes and the descendants of Spaniards, all of whom have mixed,

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but in varying proportions. The subtropical zone is quite similar, except that the Negro element is much smaller. (At the time of the slave trade the Negro's muscular strength was not held in great demand by the plantation owners of this region.) In the temperate and cold regions the Negro factor is completely absent from the racial mixture, leaving only the Spanish and Indian elements. Since, at the time of colonization, the Spanish women did not accompany the Conquistadores due to the vast distances and the constant fighting, the men mixed freely with the Indians. The result is an Indian-Spanish mixture, that is rather homogenous.

From the economic point of view, and again using the geographical groupings of tropical, subtropical and temperate, we find that the countries comprising the tropical group have one common characteristic: they are essentially one-industry countries, devoted either to agricultural or mineral production. Their cities, therefore, serve merely as centres where manufactured objects from abroad are exchanged for the agricultural and mineral products of the interior. They have no industries that can properly be called indigenous, and since "market places," which is what they really are, do not call for large concentrated populations, the cities remain small and the great mass of the respective populations live scattered throughout the interior of the respective countries.

The subtropical zone includes countries very similar to those of the tropical regions, in that they have one- or two-industry economies. However, the raw materials are processed to some degree; there is a sort of semi-manufacture of products before exportation. And with the factories have come larger cities and a more clear-cut division between urban and rural populations. What is even more important, is the fact that in this zone urban population is increasing markedly, while in the tropical zone there is little evidence of change.

In the temperate zone, that is, in the extreme south of the Continent, industries have grown up and agricultural crops are diversified. This, of course, has led to an active commercial interchange with other countries and the necessity for large cities of one or two million people. This temperate zone is much more comparable to the United States than either of the two regions mentioned before.

Of course, the quality and types of housing and nutrition differ greatly from one zone to another. Unfortunately, no numerical index can be used to show this difference, since not only are feeding habits quite diverse but the purchasing value of the money in the various countries is quite unstable and differs widely from one place to another. We, therefore, prefer to use the study made by the Latin-American Worker's Federation (Confederación de Obreros Latino-Americanos) of the amount of meat and milk that a worker can obtain for an hour of labor. Not all countries are included, but the study gives examples that are quite typical of each zone. It also demonstrates, quite well, the great difference in the standard of living between one zone and another. (Table 1.)

Accepting as an established fact, first that there are differences in racial susceptibility to tuberculosis; second, that its course is influenced by the standard

of living; and third, that the probabilities of getting infected are conditioned by the population density, we should still have to recognize the fact that these three factors have differing importance in the various zones and compensate for one another to a certain extent.

In the tropical and subtropical zones the presence of two highly susceptible racial groups, the Negro and the Indian, and of a low standard of living, which results inevitably from the type of national economy discussed before, causes a condition highly favorable to a rapid spread of the disease. On the other hand, the fact that the majority of the people are engaged in agricultural or other rural activities, resulting in low population density, diminishes the possibilities of contagion and gives tuberculosis a local character. That is, while in certain cities of this zone the level of infection is quite high, the probability of this level

TABLE 1

Purchasing value of one hour's wages for milk and meat in Latin-American countries, compared with the United States

ZONE	MILK IN LITRES	MEAT IN KGRS.
Tropical		
Ecuador.....	1	0.2
Bolivia.....	1	0.2
Subtropical		
Mexico.....	2	0.4
Colombia.....	3	0.4
Cuba.....	2	
Temperate		
Argentina.....	5	1.5
Uruguay.....	5	2.0
Chile.....	2.5	0.6
United States.....	10	2.0

becoming general is slight, considering the changes of the economy of the different zones.

In the temperate and cold zones of the south, the Indian racial strain, strongly reinforced by European blood, is more resistant to tuberculosis and a higher standard of living prevails than in the other two zones. However, there are offsetting features. Although industrialization is backward as compared to the United States, it has been taking place and cities have grown rapidly in recent years. Serious overcrowding has resulted, facilitating the contagious process of the disease. All the characteristics of a stage of maximum infection are present.

We think, therefore, that, while one part of Latin-America is undergoing a phase of increasing infection, the other presents evidence of an already established maximum infection, with the exception of a few cities where there has

been a great deal of European immigration. In these latter, tuberculosis seems to be declining.

The statistical data extant support this interpretation. Unfortunately, there are no central organizations which compile statistical data and we know that the information published by individual countries varies as to its reliability. The countries which are economically advanced issue information of good quality. However, those which are more backward present only incomplete figures and even these are not always reliable.

TABLE 2

The degree of industrialization and agricultural work according to tropical, subtropical and temperate zones in Latin-American countries, compared with the United States

ZONE	COUNTRY	PER CENT AGRICULTURAL WORK	PER CENT INDUSTRIAL WORK
Tropical or one- industry	Bolivia	88.7	1.1
	El Salvador	73	5.1
	Ecuador	—	—
	Honduras	72.4	7.7
	Haiti	—	—
	Rep. Dominicana	84.3	6.2
	Paraguay	—	—
	Venezuela	84.7	5.6
Subtropical or in- termediate	Brazil	59.4	6.7
	Colombia	62	16.9
	Guatemala	71.1	12.5
	Mexico	70.0	10.4
	Peru	62.5	17.2
Temperate or in- dustrial	Argentina	42.4	16
	Chile	34.7	19.6
	Uruguay	45	13.1
	United States	18	28.9

Data for three countries are not available and Panama is deliberately excluded because the Canal Zone creates conditions that are quite different from Latin-America in general.

Subject to the above limitations, we have prepared a table showing the percentage of the population engaged in industrial and in agricultural work for most of the countries on the Continent. In table 2 we have classified the countries according to the three zones previously mentioned, paying little attention to climatic factors, which for our purposes has little importance, but instead measuring each country against the yardstick of whether or not it belongs to a zone in which the one-industry economy predominates.

APPRAISAL OF TUBERCULOSIS IN SOUTH AMERICA

With this brief summary of the socio-economic conditions of South America as a background, we wish now to present such data as are available about the status of tuberculosis in the various countries.

We cannot give general figures for the Continent as a whole, nor for every country, since reliable statistics are often missing. Such data as are available often refer only to small groups within a given country and relate to greatly varying periods of time.

Therefore, in trying to comply with the request of the National Tuberculosis Association to report on tuberculosis in South America and to do so with something approximating standardized statistics, we sent a questionnaire to our colleagues in the various countries, asking them to report on the following topics for their respective nations: morbidity and mortality rates; incidence; results of mass surveys; amount of BCG vaccination done and any results observed; distribution of tuberculosis by age, sex, economic condition and location (urban or rural); and recent legislative measures concerned with tuberculosis, as well as other details.

Information was received from Argentina, Brazil, Paraguay, Venezuela, Ecuador, Uruguay and Peru. Information covering other countries was assembled in large part from the Proceedings of the Fifth Pan-American Congress on Tuberculosis, held in Buenos Aires in 1940, and from Dr. Luis Sayé's book entitled *Doctrina y Práctica de la Profilaxis de la Tuberculosis*. Many other sources were consulted and much valuable aid was given by Professor Raúl Vaccarezza of Buenos Aires, Professor Boettner of Asunción, Drs. Armando Sarno and Fernando Gomez of Montevideo, Dr. Isaac Pardo of Venezuela, Dr. Jorge Higgins of Guayaquil, Dr. Klinge of Peru, Dr. Reginaldo Fernandez of Brazil and Drs. Benjamin Viel and Herman Romero of the School of Public Health in Chile. We would like, at this point, to express our sincere appreciation to all these men. Without their help, this work would have been impossible.

Let us see what partial data of recent date we have been able to collect:

Argentina: The country is 3,650 kilometers in length and 1,700 kilometers in width. Its surface area covers approximately 2,987,655 square kilometers. The population in the 1937 census was 13,320,641.

National data on morbidity and mortality for the last ten years are not available. However, on the basis of such scattered local reports as have been published, we calculate that the general mortality rate for the country is 111.7 per 10,000 and the death rate for tuberculosis 10.13 for 10,000.

There were 148,841 deaths registered in Buenos Aires for the year of 1941. Of this number, 133,040 were certified by a physician and, of these latter, 13,507, or 9 per cent, were due to tuberculosis.

It is interesting to note in what relation tuberculosis stands to other causes of death. In the same year of 1941, first place was occupied by cardiac cases, 10.60 per cent; the second by cancer, 10.06 per cent; and tuberculosis was third, with 9 per cent of all deaths. The remaining causes of death varied between 6.61 and 2.90 per cent.

Also in 1941, the Argentinian Tuberculosis League X-rayed 160,000 apparently healthy persons, most of them industrial workers, and found 3 to 3.5 per cent with apparently active lesions. Examinations carried on among university students by Professor Vaccarezza gave the following figures for apparent active tuberculosis: men, 0.84 per cent; women, 0.74 per cent.

In general, in the country as a whole, Professor Vaccarezza says that he has not found any significant difference in mortality curves by age between the two sexes. For both he finds that the peak mortality is reached around 30 years of age. In Buenos Aires there is a slight difference. Men have a higher mortality than women and the peak is reached around 40 years of age.

Regarding BCG vaccination, the following information is available: by 1945, Raimondi and Urquijo had vaccinated 120,000 new-born children and 2,150 in the preschool age group. In addition, the Argentinian Tuberculosis League had vaccinated over 20,000 persons, mostly new-born infants. No complete study of the results of the vaccinations has been published, but we have some partial reports which indicate that greater resistance is evidenced by those who have received the vaccine than by those who have not.

In the legislative field, we cannot report that any important steps have been taken in regard to tuberculosis. In general, tuberculous patients receive the same social security benefits that other groups of sick people in the population receive. Better provided for are certain groups of public and private employees who belong to mutual organizations. Some private organizations have developed interesting plans in several cities and have obtained official backing.

In evaluating statistics we must not forget that in the population of Buenos Aires there is a high concentration of European elements or of descendants of Europeans, and that consequently the figures for this city differ widely from those for the rest of the country. We quote from Professor Sayago of Córdoba who says:

"It is easy to verify that the curve of tuberculosis mortality in the Argentine Republic is quite dissimilar in different provinces and cities. While in some, tuberculosis is declining, in others it maintains a high level and, finally, in still others the mortality is increasing. Among army privates tested with tuberculin there are 57.1 per cent with positive reactions among those who come from rural areas, as against 80.3 per cent among those who come from the capital city."

Sayago also reports that there are great differences between different provinces, for example, in the provinces of San Luis and Santiago del Estero there are 49 deaths per 100,000 inhabitants, while in Jujuy and Salta there are 328 deaths per 100,000. Such tremendous differences can be explained by the fact that the population density in Argentina is very low (4.4 inhabitants per square kilometer) and the majority of the population is engaged in agricultural pursuits in these low density zones where spread of infection is limited. When these same people, with their Indian racial background, group together in the large cities, as they have been doing recently, the mortality figures shoot up since they have little or no resistance.

Paraguay: The country has an area of 452,872 square kilometers, and, though there has not been a census for quite some time, the population can be estimated at a million and a half people, of which 126,915 live in Asunción.

Professor Boettner has given us epidemiological data covering some 60 per cent of the population, or about 780,000 people. He has warned us that all data concerning Paraguay, with the exception of Asunción are quite unreliable,

not only because of the deficiency of dependable statistical analysis and collection, but also because there is a lack of medical diagnosis in ascertaining causes of deaths.

With this in mind, we present, in table 3, figures on tuberculosis mortality per 100,000 people for the years 1940 to 1945.

In 1945 to 1946, 37,749 people were tuberculin-tested in Asunción. The Mantoux method was used and 95.61 per cent reactors were found. In rural areas, Doctor Buzarquis tested 1,570 persons, using only one injection of 0.1 mg. OT. He found 15.15 per cent reactors. This considerable difference in the percentage of reactors between the capital city and rural areas leads to some interesting observations on the state of tuberculosis in South America as a whole. It points to the existence of an ascending infection level that reaches massive proportions when people leave rural zones of low population density and congregate in urban centres. Since Argentina and Paraguay have a common

TABLE 3
*Annual tuberculosis mortality rate in Paraguay, and separately
in Asunción, per 100,000 from 1940 to 1945*

YEAR	ASUNCIÓN	REST OF THE COUNTRY
1940	143	28
1941	184	30
1942	144	31
1943	152	45
1944	162	47
1945	145	46

frontier, but quite different socio-economic conditions, we thought it interesting to consider the one immediately after the other and deliberately put them in this order.

Also, in connection with mass surveys, in a study of supposedly healthy segments of the population and of known contacts to open cases made in Asunción in 1946, 1.32 per cent of active tuberculosis was found. This percentage was, in turn, broken down as follows:

Primary infection.....	0.44 per cent
Minimal reinfection lesions.....	0.22 per cent
Advanced reinfection lesions.....	0.66 per cent

Among causes of death in Asunción in 1940 to 1941, tuberculosis ranked first and was followed by bronchopneumonia or pneumonia, and then by gastrointestinal diseases, especially diarrhea in children under 2 years of age.

The peak mortality for tuberculosis occurs between the ages of 20 and 40 and is higher in women than in men.

BCG vaccination is practiced only in Asunción, where the multipuncture method of Rosenthal is used. To date, 5,000 persons have been vaccinated by this method, but results cannot yet be judged.

Regarding legislative measures, the state offers some protection to workers who contract tuberculosis through its compulsory *Ley de Previsión Social*. By its provisions, a person with confirmed tuberculosis receives his regular salary for a six-month period, which time may be extended to a year and a half if it can be demonstrated that there is a chance for a cure. If, after the six-month period, the case is believed incurable, the patient is entitled to apply for a life-time disability pension.

Government employees who contract tuberculosis or leprosy do not come under this act. There is a special law giving them compensation, which may not be less than 50 per cent of their regular salary, for at least two years. If a cure has not been effected by this time, they are entitled to retire on the same basis as a person who has served out his full term of years in the Government Service.

To receive benefits under either of the above laws, a person must have taken a medical examination which includes a tuberculin test and an X-ray film.

It should be pointed out that private organizations in Paraguay are also doing very valuable work. However, there is a grave deficiency in the number of beds available for tuberculosis.

Uruguay: With its 186,926 square kilometers it had, according to the official census of 1937, 2,093,333 inhabitants and a density of 11.20 persons per square kilometer, which is the highest in Latin-America. There is a strong current of European immigration. Uruguay is probably the only South American nation in which tuberculosis is positively decreasing throughout the country as a whole.

The average mortality rates for tuberculosis for the entire country are as follows:

1930 to 1934, per 100,000 inhabitants,	134.2
1935 to 1939, per 100,000 inhabitants,	112.6
1940 to 1943, per 100,000 inhabitants,	109.3

The peak mortality is reached between 15 and 30 years of age.

A survey made of known contacts to open cases of tuberculosis revealed 12.35 per cent of active cases. In the population at large, a similar survey revealed the following information:

Industrial workers.....	3.2 per cent active tuberculosis
Army privates.....	2.1 per cent active tuberculosis
Bank employees.....	3.3 per cent active tuberculosis
Grammar school children.....	1.7 per cent active tuberculosis

As we have seen in other countries, the morbidity varies according to zone, whether urban or rural. The same holds true even in Uruguay, where the highest population density in South America is found. The infection levels in Uruguay, as measured by tuberculin-testing surveys, are as follows:

Northern zone: Living conditions are substandard, there is undernourishment and overcrowding.

Tuberculin reactors—adults.....	62.2 per cent
Tuberculin reactors—children.....	25.2 per cent

South-western zone: Living conditions are normal, nutrition good and there are no large urban centres close by.

Tuberculin reactors—adults.....	45	per cent
Tuberculin reactors—children.....	26	per cent

South-eastern zone: Living conditions mediocre, nutrition deficient, and constant movement between this zone and large urban centres.

Tuberculin reactors—adults.....	60	per cent
Tuberculin reactors—children.....	37.1	per cent

Central zone: Living conditions mediocre, nutrition deficient, completely rural.

Tuberculin reactors—adults.....	78	per cent
Tuberculin reactors—children.....	67	per cent

City of Montevideo:

Tuberculin reactors—adults.....	81	per cent
Tuberculin reactors—children.....	63	per cent
Tuberculin reactors—infants.....	9.7	per cent

BCG vaccination has been actively carried on, and in 1945 there were 125,739 persons vaccinated, of which, 15,700 were under adequate control. According to Professor Fernando Gomez, it can be said that among the vaccinated the morbidity and mortality is one-fourth of that found in the control group.

The control program in Uruguay has been developed very satisfactorily through the following organizations: the Anti-Tuberculosis Prevention and Aid Service of the Department of Public Health; the Department of Public Education, which maintains a Tuberculosis Institute, complete with dispensary, lying-in hospital for tuberculous women and a vaccination centre—all in the medical school; the War Department, which maintains centres where epidemiological studies are made and which provides a certain number of beds; the Municipality of Montevideo, which provides health examinations and X-ray examinations for domestic servants, food handlers and people who work in the transportation industry; and, finally, the Institute of Inter-American Affairs, which has aided the Department of Public Health in building and equipping three health centres in the most important cities of the country.

All in all, with its 1943 tuberculosis mortality of 2,631 and its 2,600 beds, Uruguay has its tuberculosis problem under control to a degree not equalled anywhere else in South America. Moreover, at the present time there are 1,900 more beds under construction, which will bring the total number to 4,500.

As regards financial aid for tuberculous patients, in 1934 a law was passed granting three years of rest with full salary to any Government employee who contracted tuberculosis. In 1945 a National Permanent Fund for the Fight against Tuberculosis was created, with contributions coming both from the state and from private sources. The Fund is to be used exclusively for needy families of tuberculous patients, either hospitalized or confined to bed in their own homes.

There are many other activities that we have not mentioned which are carried on by the Anti-Tuberculosis Prevention and Aid Service of the Department of

Public Health, such as child preventoria, rehabilitation centres, etc. All in all, Uruguay has one of the most complete and interesting tuberculosis programs in South America.

We wish to thank Professor Fernando Gomez who has the Chair of Tuberculosis in Montevideo and Dr. Armando Sarno, *Director del Servicio de Asistencia y Preservación Anti-Tuberculosa*, for the great aid they have given us in sending us very complete data for their country.

Ecuador: With an area of 816,414 square kilometers, the country has approximately three million inhabitants. According to Dr. Jorge Higgins, who has given us the information for this section, national statistics are incomplete and defective. Only since 1942, he says, have any reliable demographic studies been made. For this reason, Doctor Higgins has limited his information almost exclusively to Guayaquil, where he lives and does excellent work.

In 1946, Guayaquil had 216,615 inhabitants and in 1945 its tuberculosis mortality was 416.5 per 100,000.

The antituberculosis dispensary in Guayaquil has tuberculin-tested about 10,000 people and found 84.3 per cent reactors.

In the last two years, considerable work has been done with BCG vaccination in Guayaquil. Higgins has become so enthusiastic about the tentative results of the program that to-day he is vaccinating all babies born in the maternity hospitals and all nonreactors that come to the Mother and Child Centres.

In Quito vaccinations were begun in 1940, and by 1946, 4,000 children had been vaccinated. At first oral and subcutaneous routes were tried but at present the Rosenthal technique is used. Some reports on the results in Quito have been published by Dr. Luis Andrade, which we feel are of interest in spite of the fact that they are not complete and give figures on general infant mortality rather than on specific tuberculosis mortality. The percentages refer to the one to 3 year age group. The total mortality was 9 per cent in vaccinated and 32 per cent in nonvaccinated.

At the present time, two big centres of epidemiological research, one in Quito and the other in Guayaquil, are being completed. Beds are being provided in both cities and the Public Health Department is putting into effect a comprehensive five-year plan that should give impetus to the tuberculosis campaign in Ecuador.

Peru: The population of the country is 6,500,000 and it has an area of 1,358,000 square kilometers.

According to the information which Dr. Leonidas Klinge obtained for us from the Tuberculosis Department of the Public Health Service, the country is going through a period of massive infection, characterized by a high tuberculosis mortality. There are large numbers of reactors at all ages, with an especially high percentage in the first two years of life, and a large number of cases both clinical and nonclinical, active and progressive. (Table 4.)

Tuberculin-testing in Lima dispensaries revealed 30 per cent reactors in the age group from birth to 2, 50 per cent in the age group 2 to 16 and 85 per cent at ages 16 to 60.

Mass surveys of supposedly healthy segments of the population have given results of more than 3 per cent active nonclinical tuberculosis.

As to extent, 30 per cent were minimal, 40 per cent moderately advanced and 30 per cent far advanced.

In the same survey a study was made of housing conditions, salaries and nutrition of the tuberculous patients found. Housing conditions were good in 10 per cent, fair in 50 per cent and bad in 32 per cent. In terms of real wages, 25 per cent had a sufficient income, while 75 per cent had an insufficient income. Only 20 per cent had good nutrition, 50 per cent fair nutrition and 30 per cent were classified as having bad nutrition.

In 1941, the National Anti-Tuberculosis Service was created. Its stated purposes were to do preventive work and also to provide medical care for patients. The Service directs and coördinates all activities in the tuberculosis program. It has also begun to collect and centralize tuberculosis statistics. Moreover, the Service is working indirectly towards tuberculosis control by

TABLE 4

Tuberculosis mortality per 100,000 in various Peruvian cities in 1945

CITIES	TUBERCULOSIS MORTALITY RATES	CITIES	TUBERCULOSIS MORTALITY RATES
Tacna	625	Chiclayo	269
Callao	483	Arequipa	418
Mollendo	449	Cuzco	264
Pisco	348	Puno	244
Lima	357		

attempting to improve housing, diets and wages. It also brings health and sanitary education to the people.

At present the means with which the Service has to work are limited, especially as regards the treatment phase of their program. However, there is a plan under way which will provide for 6,470 beds to be distributed in general hospitals, regional sanatoria and preventoria for children, scattered throughout the country. In addition to this, 28 dispensaries will be constructed in various parts of the nation.

BCG vaccination has been carried on since 1933 by the Tuberculosis Department of the Public Health Service, but we have been unable to secure any data concerning the results of the program.

Mexico: In spite of the fact that this study was to be limited to South America, we wish to take advantage of our contacts with Dr. Ismael Cosío Villegas, Professor of Tuberculosis in Mexico, to include some valuable information on tuberculosis in his country. We feel that this information will help to round out the report.

Mexico's 1930 census reported that the population was 16,552,722. According to official estimates, by 1939 the number had risen to 19,478,791. Of this

latter number it is estimated that one-third lives in urban areas and the rest in rural areas.

It is interesting to note that, in the general budget of \$445,265,943.78 for 1939, \$16,500,000 were allotted for Public Health work.

Regarding morbidity and mortality, Doctor Cosío Villegas estimates that in 1939 there were some 300,000 cases of tuberculosis and some 30,000 deaths caused by tuberculosis in the country.

A tuberculin-testing program carried out among school children in Mexico City revealed 49 per cent reactors. The majority of the children were around 12 years of age.

A mass survey, using photofluorography, carried out among policemen, workers applying for health certificates and university students, resulted in the finding of 1.39 per cent of active cases. All in all, the survey covered 250,000 people.

The main work of the control program is carried on by a Department of the Ministry of Public Health and Medical Assistance, which has its own funds and which carries on direct programs of treatment and also does indirect control work through such organizations as the School of Public Health, Nutrition and Hygiene and Sanitary Engineering. The Department runs seven tuberculosis dispensaries in Mexico City and thirty more in other parts of the country. It has at its disposal about 1,350 beds, the majority of which are in the Federal Capital and the rest in other principal cities. At present three more 300-bed sanatoria are being constructed.

There are several preventoria for children and a system of foster-homes for children is also used as a protective measure.

BCG vaccination is being carried on with some intensity but no results are available.

It is interesting to note that in a five-year period the sale of antituberculosis stamps has produced \$6,500,000.

Mass surveys are being constantly carried on for the purpose of making epidemiological studies in two permanent centres where 4 x 5" film is used and in two mobile units where the 35 mm. method is practiced.

Up-to-date data for the remaining South American countries are not available, in spite of the fact that we solicited information immediately upon receiving the invitation to make this study. To use the material published in the various medical journals and especially that given in the Proceedings of the last Pan-American Congresses of Tuberculosis would lengthen this study enormously, without particularly changing the total picture for Latin-America that we have tried to give. These are our reasons for omitting many countries of general importance. However, before presenting our conclusions we want to speak briefly about Brazil and Venezuela and then consider in somewhat detailed form the situation in our own country, Chile.

Brazil: Brazil occupies almost half of the South American Continent. It covers 8,611,857 square kilometers and has 45,000,000 inhabitants.

In spite of the fact that tuberculosis mortality is very different in different regions of the country—there are agricultural regions of low density, areas which have recently been industrialized and urban areas of long standing—an average death rate of 250 per 100,000 inhabitants for the country as a whole can be postulated. This figure also takes into account the differences in racial groups in Brazil: Negro, Mulatto and white.

In their interesting book *Roentgenfotografia*, Manoel de Abreu and Aloysio de Paula present certain information which we wish to quote.

In 1940 the Thoracic Centres of Rio de Janeiro X-rayed 12,000 Municipal employees, candidates for jobs and patients in the hospitals and Municipal Clinics who came from diverse social groups. They found 2.5 per cent active cases. On this basis, Abreu and de Paula estimate that there are about 50,000 people with active tuberculosis in Rio de Janeiro.

In the cases making up the 2.5 per cent in the survey, 1.60 per cent were moderate or far advanced with cavities. An additional 5 per cent in the survey had apparently inactive reinfection type tuberculosis.

As regards the presence of clinical symptoms in the cases uncovered by the survey, there was a proportion of one person with symptoms for every 10 without. Among the patients with cavities, for every 4 who were cognizant of their symptoms there were 31 who had no idea that they were ill.

The type of lesion seen was usually exudative, especially in the 20 to 30-year age group.

In the Brazilian contribution to the Fifth Pan-American Congress on Tuberculosis, held in 1940, Abreu and de Paula point out that figures on tuberculin-testing are very incomplete from a national point of view. However, such results as are available indicate a very high percentage of reactors—over 90 per cent among adults in large cities. As contrasted to this, they refer to a rural town, Jacana in the province of Sao Paulo, where reactors only reached 53.1 per cent and the distribution by ages was as follows:

Up to 3 years.....	11.1 per cent
Preschool children.....	21 per cent
School children.....	30 per cent
Young adults.....	66.4 per cent
Adults between 26 and 65.....	80.1 per cent

After this paper was already written, we received some interesting information about the tuberculosis situation in Brazil from Dr. Reginaldo Fernandez, President of the Tuberculosis Society of Rio de Janeiro. The information he presents on BCG vaccination and the Brazilian Anti-Tuberculosis Organization is as follows: BCG vaccination was begun in 1927 by the Brazilian Anti-Tuberculosis League. By 1944 they had vaccinated in Rio de Janeiro 161,663 new-born infants, of whom 25.57 per cent were followed-up. Vaccinations done in other parts of Brazil raised the total number of vaccinated to approximately 350,000.

Tuberculosis control activities are centered about the National Tuberculosis Service whose main offices are in Rio de Janeiro and which has branches in all

principal states of the country. It deals with prevention of the disease, and with the orientation, coördination and financing of public and private tuberculosis institutions. To date the service has built 21 hospital-sanatoria, one for each state, 55 dispensaries and 13 tuberculosis centres where tuberculin-testing is done. At present the service is constructing special tuberculosis pavilions in the general hospitals of the country.

Venezuela: The country's area measures 912,050 square kilometers. The present population is estimated at a little over four million. According to a survey made in 1937, the racial composition of the country was as follows:

Indian-Negro-white mixture.....	85 per cent
Indian.....	10 per cent
White.....	5 per cent

As in the case of Doctor Fernandez, the information on Venezuela sent us by Dr. Isaac Pardo of Caracas arrived too late to be included in this report. We, therefore, are using the statistics which Doctor Pardo presented to the Fifth Pan-American Congress on Tuberculosis in 1940.

In urban centres the average tuberculosis mortality is 321 per 100,000 inhabitants. Throughout the country as a whole, and depending upon the locality, mortality rates vary between 210 and 470 per 100,000. In localities where the incidence is high, tuberculosis accounts for as much as 23.16 per cent of the total mortality.

Epidemiological surveys made in Caracas and in rural areas among supposedly healthy population elements gave the following percentages of active cases:

Urban population.....	2.43
Semirural population.....	1.52
Rural population.....	1.02 to 2.2
Indian population.....	0.98
Population in petroleum areas.....	1.51

According to age, the number of active cases is high in infants. It diminishes in the 10 to 19-year-old group and goes up again from this point to reach a peak at 30 years of age.

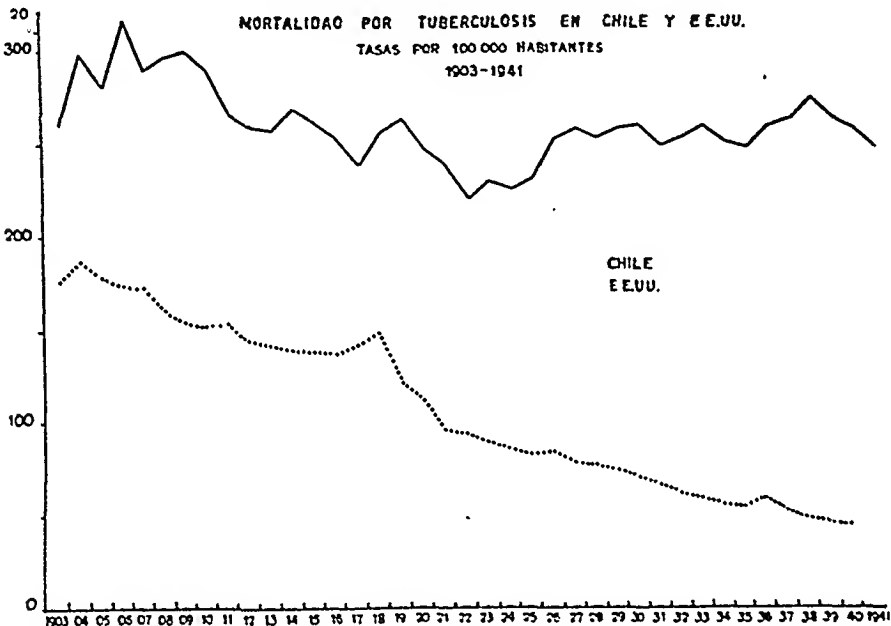
In tuberculin-testing surveys made in urban areas, over 20 per cent of new-born infants were reactors. By 14 years of age, the percentage went up to 51 and in persons over 14, it reached 83.2 per cent. In rural areas, infection is much lower and may be broken down as follows:

Rural population.....	27.3 per cent
Indian population.....	25.9 per cent
Petroleum industrial area up to 14 years	40.6 per cent
after 14 years	75.1 per cent

We may deduce from these figures that, as in the rest of South America, tuberculosis has two fundamental aspects. In rural or semirural areas of slight population density, where the inhabitants come into contact with urban centres, it is in an ascending phase; in the urban centres themselves and in industrial areas it is epidemic and of massive proportions.

As Doctor Pardo pointed out, one of the important features responsible for the spreading of infection, which is often overlooked, is the frequency with which bovine tuberculosis is found in animals stabled either within or close to urban centres. He says that it is especially prevalent in imported herds.

Chile: Chile is a long strip of land, lying between the Cordillera of the Andes and the Pacific Ocean. Its width varies from 170 to 300 kilometers and its length is 4,222 kilometers. In area it covers 741,767 square kilometers and its population is 5,400,000. Almost one-fifth of this entire population lives in the province of Santiago and the capital city itself has around 1,000,000 inhabitants, excluding surrounding towns.



GRAPH 1. Tuberculosis mortality rate per 100,000 in Chile and in the U. S. A. from 1903 to 1941.

Between 1903 and 1946 the tuberculosis death rate of 260 per 100,000 has remained fairly constant, as shown in graph 1. The rates according to age groups are presented in graph 2. Deaths from tuberculosis account for 11.9 per cent of the total mortality. The actual figure is 15,000 annual tuberculosis deaths. In the age group of 15 to 50, the most productive years for the individual, tuberculosis accounts for 32.4 per cent of all deaths. These figures are national averages and vary considerably from zone to zone. In agricultural areas of low population density, the mortality is as low as 100 per 100,000 inhabitants; in a few exceptional urban centres it goes as high as 400 per 100,000 inhabitants.

Morbidity rates for Chile can be determined with a good deal of exactitude. This is due to the fact that general statistics are quite reliable in this country

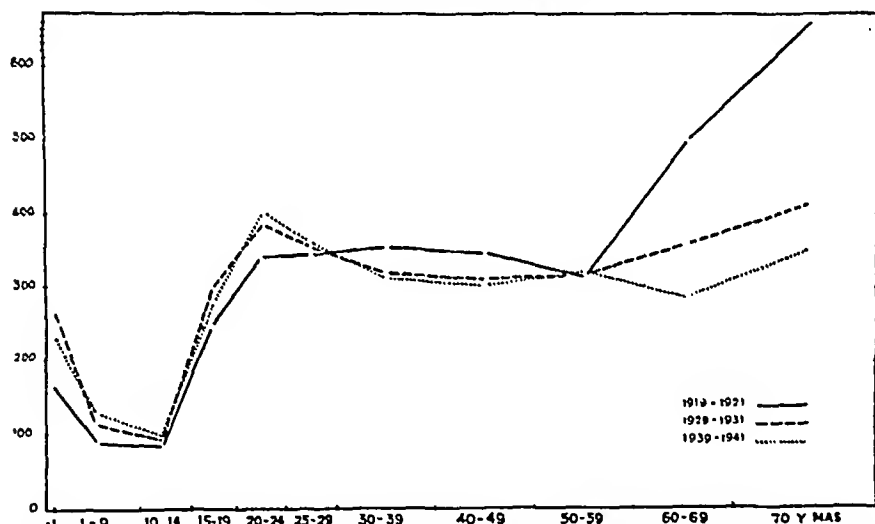
and also because, since 1937, the preventive medicine law, which calls for obligatory health examinations of all workers for the purpose of discovering cases of tuberculosis, syphilis or cardiovascular diseases, has been in force.

Between 1938 and 1943, 600,000 workers of both sexes and 83,000 domestic workers were examined. The results are very useful in establishing morbidity rates in Chile.

In a group of 25,566 employees who were examined, we found active tuberculosis in 3.32 per cent of men and 3.81 per cent of women. In a group of 19,197 workers in the city of Santiago who were taking their regular health examination, we found 3.6 per cent of active tuberculosis (see table 5).

One of the most favorable results of the obligatory health examinations has

MORTALIDAD POR TUBERCULOSIS Y EDAD EN CHILE
TASAS POR 100 000 HABITANTES
PERIODOS 1919-1921, 1929-1931 Y 1939-1941



GRAPH 2. Average annual tuberculosis mortality rates per 100,000 in Chile for three periods: 1919 to 1921, 1929 to 1931 and 1939 to 1941.

been the complete modification of the type of tuberculosis we see and treat nowadays. While in the out-patient departments of our hospitals we encounter over 50 per cent of the cases in an advanced state of the disease, among the people who come spontaneously or who are screened in the regular health examinations, 38.6 per cent of the cases are minimal and 42.5 per cent are moderately advanced. The remaining percentage is composed of inactive reinfection type cases and of advanced cases.

Investigations made among 3,420 students in the 8 to 15-year-old group, all of them residents of a poor neighborhood in Santiago, 70, or 2 per cent, had active tuberculosis (table 5). Of the 70 cases, 69 per cent had only primary lesions.

According to figures prepared by Doctor Viel in which he used the usual statistical basis, we can estimate that there are 7.4 active cases of tuberculosis

for each annual tuberculosis death, which brings the total number of active cases of tuberculosis in Santiago to 26,665.

As regards morbidity in urban areas, tuberculin-testing reveals almost 100 per cent reactors in the adult population. In school children where investigations are made quite frequently throughout the country and with more or less

TABLE 5
Tuberculosis morbidity in Santiago, Chile
Survey of 1942 (rate by hundred)

AGE IN YEARS	STUDENTS, GRAMMAR AND HIGH SCHOOL	EMPLOYEES	WORKERS
- 8	2.3	—	—
9-10	1.8	—	—
11-12	1.5	—	—
13-14	2.5	—	—
15-19	3.9	4.1	3.7
20-29	—	4.8	4.1
30-39	—	2.9	3.1
40-49	—	2.2	2.7
50-+	—	0.8	2.3
Total.....	2.0	3.5	3.6
Number examined	3,420	25,566	19,197

TABLE 6
Number and percentage of tuberculin reactors among
children of poor families in Santiago, by ages

AGE IN YEARS	NUMBER EXAMINED	TUBERCULIN REACTORS	
		Number	Per cent
7 to 8	752	450	59.8
9 to 10	1,065	749	70.3
11 to 12	1,017	756	74.3
13 to 14	510	394	77.2
15 to 16	76	57	75.0
Total.....	3,420	2,406	70.3

the same results, we find the figures presented in table 6; they specifically relate to children of poor families from Santiago.

Under our direction, Dr. Alfredo L. Bravo surveyed a small group of country people quite isolated from urban centres and found only 30.2 per cent reactors, which seems to indicate that there are rural zones in Chile relatively free from tuberculosis, as contrasted to highly infected urban areas.

As regards surveys made of contacts to open cases, we have the studies made by Doctors Raddatz and Fernandez who also worked under our direction in the Hospital del Salvador. Among families of tuberculous patients in the hospital

of all ages, they found 17.1 per cent of active cases. Most of the group examined belong to an economically modest or poor social group. Of those under 15 years of age, the percentage of active cases rose to 21.9 per cent.

Viel made a similar survey of contacts to tuberculous patients who belong to a higher social and economic class, namely, civil servants and private employees. In this group, he found 11.1 per cent of active tuberculosis.

We are short of beds in Chile. With an annual mortality of at least 15,000, we have only 3,600 beds distributed among general hospitals, special hospitals and sanatoria. These are scattered throughout the country.

The tuberculosis control program is directed by the Workmen's Insurance Fund (*Caja ó Instituto de Previsión*) and by the Free Social Assistance Bureau (*Beneficencia y Asistencia Social*). Both of these organizations maintain clinics in all important cities of the country.

As we mentioned before, since 1937 there has been in effect the preventive medicine law, written by the then Minister of Health, Dr. Eduardo Cruz Coke, which made health examinations obligatory for all applicants for work and which further provided for an annual examination of workers. The law also deals with compensation and provides that tuberculous patients who are considered curable are to be given a bed or ambulatory treatment by the insurance organization to which they belong and that during the time of cure they are to receive their full salaries.

Before 1937 the Workmen's Obligatory Insurance Corporation (*Caja de Seguro Obligatorio*) which was financed chiefly by employers, then by the worker and finally by the State, could not handle the tuberculosis problem in a satisfactory way, due to the multiplicity of obligations which this Corporation had, such as general medical care and disability and old age pension. The new law provides for a contribution on the part of the employer of 1 per cent of the monthly salary of each employee, plus 2.5 per cent of the gross income received by the various Government Insurance Institutions, to finance the tuberculosis control program.

The results of the new law have quickly become evident. The opportunity for prompt diagnosis and treatment has permitted us to obtain cures between 68 to 72 per cent using the usual therapeutic methods, as against the 30 to 40 per cent that previously obtained with cases that came looking spontaneously for treatment.

Naturally, the new law has not solved the tuberculosis problem in Chile. Moreover, it has its disadvantages. It has created a new and privileged class of curable patients whose economic and therapeutic problems are solved for them. However, the benefits of the law are not available to advanced cases which continue disseminating the disease day after day. These advanced cases cannot even find a bed since a high proportion is occupied by the minimal and moderately advanced clients of the various insurance funds. Also, destitute people are absolutely outside of the preventive medicine law, since only workers come under its protection.

Since 1930, there has been a special Chair of Tuberculosis in the Medical

School. In that same year the Chilean Tuberculosis Society was created. Through its initiative the official classification of the National Tuberculosis Association was adopted in Chile three years ago.

At the present time among Public Health Authorities there is a tendency to unify and centralize all activities in the tuberculosis control program and to devote large sums of money to increase the number of beds now available. In this connection, we wish to point to the valuable aid of the Department of Inter-American Affairs which has just given the Social Assistance Bureau a new and completely equipped 500-bed hospital. It has aptly been named Trudeau in homage to the great American visionary who introduced the sanatorium treatment in this Continent.

CONCLUSIONS

1. South America is undergoing an epidemic stage of tuberculosis. In sparsely populated areas the infection level is rising, while in the few crowded urban areas, where there are large groups of Europeans or their descendants, it has begun to decline and an endemic phase has begun.

2. By and large, national statistics are lacking for South America and the data that are available refer only to small areas or groups. There is also a lack of standard statistical methods, preventing the compiling of reliable conclusions.

3. There is a lack of means and resources absolutely necessary for the successful prosecution of the fight against tuberculosis in South America.

4. Social and economic protection is insufficient.

5. It would be desirable and of great aid if a Pan-American Conference on Tuberculosis were held to prepare a uniform system of collecting and classifying statistical information. This would allow us to speak in a common language and to understand one another better.

CONCLUSIONES

Tuberculosis en Sud-América

1. La América del Sur se encuentra en el período epidémico de la tuberculosis. En las zonas poco pobladas el coeficiente de infección va en aumento, en tanto que en las pocas zonas urbanas hacinadas donde hay numerosos grupos de personas de natalidad o de ascendencia europeas, ha comenzado a bajar y se ha iniciado la fase endémica.

2. En conjunto, no hay estadísticas nacionales para Sud-América, y las disponibles sólo comprenden pequeñas zonas o grupos. También faltan técnicas estadísticas depuradas, lo cual impide la compilación de conclusiones fidedignas.

3. Para la lucha con éxito contra la tuberculosis en Sud-América hacen falta los medios y recursos absolutamente necesarios.

4. La actual protección social y económica es insuficiente.

5. Convendría y ayudaría mucho la celebración de una Conferencia Panamericana de Tuberculosis que elaborara un sistema uniforme para la colecta y clasificación de las informaciones estadísticas. Esto nos capacitaría para hablar el mismo lenguaje y entendernos así mejor.

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THE TUBERCULOSIS PROBLEM IN THE PHILIPPINES¹

The Rôle of the Philippine Tuberculosis Society and Other Agencies and the Present Postwar Organization

MIGUEL CANIZARES²

The paramount health and socio-economic problem of gigantic proportions in the new-born Republic of the Philippines is tuberculosis. Now, in a so-called era of peace, tuberculosis kills at the rate of four lives every hour round the clock. Due to it alone, the state loses one and a half billion dollars a year. From the moment the first bomb fell on Pearl Harbor, two wars were unleashed on the Philippines—one, fought with shell, shrapnel and other known infernal implements of death; the other, in which hunger, wartime living conditions, parasitic infestation and moral and physical tension had to be borne, like a cross, so that subsequent invasion by disease could step in with the utmost ease.

Prewar tuberculosis death rate among Filipinos was 230 per 100,000, five times the 1945 rate for the U. S. Now this death rate is certainly higher. Where there are at least 500,000 cases of tuberculosis among the 18,000,000 population to-day, there are not more than a total of 1,200 institutional beds now available throughout the Philippines for this disease.

The Philippines has a total area about half the size of Texas. In population, its 18,000,000 inhabitants equal the combined populations of New Jersey and New York states.

To New Jersey's four million people, at least 4,203 beds (1942) for tuberculosis are available. In the whole Philippines, with a death rate five times as high, not more than 1,200 such beds can be found. Even before the war, this figure has never been exceeded.

In the Philippines, tuberculosis has headed the list of deaths for decades. Not even malaria can topple it from its pedestal. At war's outbreak, field surveys in 1940 placed moribidity at 6.22 per cent, or 1,119,600 suspect tuberculosis cases. If half of these cases did not survive the war and if no new cases have cropped up meanwhile, at least 500,000 cases are probably still alive to-day. That figure is the minimum that can be arrived at.

Why is this so? What local conditions obtain which tend to make the disease so prevalent and the campaign against it so limited in the Philippines?

Two organizations, which, just before the war, had some sort of mutual understanding, are concerned with antituberculosis activities—a voluntary agency, the Philippine Tuberculosis Society, and the government outfit, which is called the Tuberculosis Control Section under the Health Bureau. The Philippine Tuberculosis Society was affiliated before the war with the National Tuberculosis

¹ Presented before a joint session of the Medical and Public Health Sections at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 20, 1947.

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Association and *L'Union Internationale Contre la Tuberculose*. There was an arrangement that the Philippine Health Bureau unit would take care of health statistics and case-finding in field surveys, while the Philippine Tuberculosis Society was to attend to the home and institutional management of cases. The educational work was jointly undertaken by both agencies. To this effect, the Society operated 4 provincial tuberculosis pavilions, 14 dispensary clinics and a central sanatorium, known as the Quezon Institute. On the other hand, the Health Bureau ran a dispensary in Manila, 150 hospital beds for advanced cases and mobile X-ray units for field surveys. These combined agencies examined by fluoroscopy and film a total of 510,843 persons in 1940, or approximately 2.8 per cent of the population.

A BIT OF HISTORY

The Philippine Tuberculosis Society was founded in 1910 by a small group of civic-minded citizens. Initially it ran two small clinics in the slum districts of Manila, but gradually its activities expanded until it was able to open a sanatorium in the outskirts of Manila in 1918. The sanatorium at first consisted of a few nipa huts or ramshackles. Year by year new additions were built until, in 1935, there were some 27 cottages and huts. A diagnostic X-ray unit was acquired in 1927, and, in 1929, 17 patients were under pneumothorax therapy. Two years later, phrenic nerve operations and thoracoplasty were introduced in the Islands. Collapse therapy found such wide acceptance that at war's outbreak the Quezon Institute alone had 1,547 pneumothorax patients. Intrapleural pneumonolysis was introduced in 1937. The Philippine Tuberculosis Society and the Quezon Institute started sending members of its staff abroad, especially to the United States, for advanced training.

The sanatorium operated by the Philippine Tuberculosis Society was renamed the Quezon Institute in 1938 after its sponsor, the late Manuel L. Quezon, who later died at Saranac Lake. It may be stated here that the late President Quezon was as interested in tuberculosis as the late President Roosevelt was in infantile paralysis. He it was who sparked the antituberculosis campaign in the Philippines. Under Quezon's administration the sweepstakes law took effect, most of the proceeds of which were set aside for use in the campaign against tuberculosis, besides proceeds from Christmas Seals sales.

Since 1938 the activities of the Philippine Tuberculosis Society steadily expanded. Dispensary clinics and pavilions were opened in populous areas of the Islands. The wooden and nipa structures of the sanatorium gave way to modern concrete buildings with enough room to house 1,400 patients. A planigraph unit was operating from 1939 to the outbreak of the war; clinical and research laboratories and a medical library were founded; an orthopedic service was established; a powerful G. E. apparatus with a miniature 4 x 5" X-ray unit was acquired in \$940; and a scientific publication was issued semi-annually containing the results of researches by the staff. Since 1938, it has begun training physicians sent by the Tuberculosis Control Section of the Health Bureau in tuberculosis work for a minimum period of two years. Undergraduate medical students from three

local medical colleges and nurses from schools of nursing also received clinical instruction and training in tuberculosis and other chest diseases. Large industrial firms were starting to have regular X-ray check-up of their employees, and government employees, school teachers and students as well.

On this organization, which gave promise of becoming nation-wide in scope, burst the Pacific war like a thunder-bolt from the blue.

PREDISPOSING FACTORS

The following factors contribute to the prevalence of the disease in the Islands:

(a) *Poor housing*: Housing was a prewar problem in itself. More than 300,000 homes were destroyed as a result of the fighting and bombings during the Pacific war, making the problem much more acute. Whole families have to double up, not in houses, but in makeshift sheds, shacks and lean-tos (the *barong-barong*) without sanitary facilities. In the razed areas of Manila and its suburbs, it is not uncommon to find three or four families squeezed into a shed measuring four by five yards, which leaks like a sieve during the rainy season and which is as hot as an oven during the summer months. Thus, spread of infection by close and continued contact is easy. The War Damage Commission could do a lot by hastening the settlement of claims, although an individual claimant cannot get more than \$500.00.

It must be mentioned here that whole communities have been wiped out in some areas, the majority of their inhabitants massacred or maimed. In Manila virtually every federal building has been demolished, century-old historic buildings gutted, and churches, museums and libraries burnt down. There is no question but there is a dearth of public buildings and private dwellings in the entire young republic to-day.

(b) *Malnutrition*: Even before the war it was an admitted fact that the Filipino race was so undernourished that every year beriberi killed more infants than did respiratory diseases. During the forty months of Japanese occupation, not only did no imports reach the Philippines due to the blockade but the countryside likewise was stripped to feed and maintain upwards of one million unwelcome guests (the Japanese Imperial Army had no quartermaster supplies to speak of). The Japanese saw to it that their troops lived off the fat and meat of the land, not caring whether the civilians starved. Hence, avitaminosis reared its head, and malnutrition contributed to the death of thousands.

Even now when nutrition is better, the high cost of living (the purchasing value of the peso is only one-fifth of its prewar level) is still taking its toll. Statisticians are agreed that for the next few years the cost of living will remain higher than prewar standards.

(c) *Parasitism*: Intestinal parasitism infests about 70 per cent of the population. Ascariasis, schistosomiasis, hookworm disease, trichinosis and amebiasis are the most important diseases from parasites that infest Filipinos. The ascarids, hookworm, schistosomes and strongylids, as they pass through the lungs in their life cycle, may cause some injury to the pulmonary tissue in their sojourn to respective habitat in the human body. Whether in this manner they predispose

the lungs to subsequent lodgment of the *Mycobacterium tuberculosis* has not yet been fully ascertained.

It is a fact though that wide-spread parasitism in the Islands contributes not only to the production of secondary anemia but so lowers the resistance of the human host that either latent tuberculous foci or other intercurrent diseases readily break out.

(d) *Dust and fly problem:* These two problems are peculiar to the tropics—as the mosquito problem is. Tropical dust is the most abundant in the world. Philippine highways were mostly concrete or asphalted before the war, but the Japanese never did any maintenance, and thousands of heavy U. S. Army vehicles have pulverized the best of the asphalted roads during the past two years. The dust of the highways, carried away by tropical winds, gets into your eyes, your nostrils and into your every pore. Hence, respiratory diseases are frequent during the dry months, and may activate many a quiescent tuberculous focus.

As for flies, they can be found in droves every day of the year. With garbage and sewage disposal extremely inadequate after the war, food, milk and water contamination plays a considerable rôle in the spread of infectious diseases.

(e) *Difficult living conditions:* Apart from housing, the traditional low wages prevailing in the Orient and the high prices of food and all other commodities contribute to weaken constitutional resistance as a result of malnutrition. Filipinos are never milk drinkers, for, in a large majority, fresh milk produces either diarrhea or tympanism.

Wages are low and the common laborer earns an average of \$1.50 a day. Physicians in the health service in charge of a county receive not more than \$75 a month; clerks and teachers about \$65 a month.

Is it any wonder, then, that the children are so undernourished that they are an easy prey to tuberculosis and other contagious diseases?

It must be stated here in passing that World War II's aftermath will be felt in the Islands for the next decade. While vital statistics for the whole Philippines are incomplete, the tuberculosis prevalence in the city of Manila, according to the Philippine Health Bureau, has risen from the prewar figure of 9.07 per cent to 21.84 per cent, or an increase of 251 per cent. Last year, there were 2,144 deaths due to tuberculosis in Manila, or a mortality rate of 280 per 100,000 for the city. At war's end in 1945, 11,258 cases were found by the Health Bureau in the same city, out of 51,550 fluoroscopic and X-ray examinations, or a prevalence of 21.84 per cent.

PREWAR ACTIVITIES

The Philippine Tuberculosis Society's fourteen dispensary clinics, four provincial tuberculosis pavilions and the Quezon Institute, for a twelve-month period from 1940 to 1941, reported the following activities:

Total dispensary attendance	219,700
(examined by fluoroscopy, miniature or regular X-ray film)	
Home visits	114,620
Artificial pneumothorax insufflation	66,930

Other major and minor operations (at Quezon Institute).....	1,109
Laboratory examinations.....	65,455
Number of pneumothorax patients (at Quezon Institute).....	1,547
Number of admissions (at Quezon Institute).....	1,236
Number of discharges (at Quezon Institute) of which 61.5 per cent had positive sputa and 38.5 per cent had negative sputa.....	1,146

On the other hand, the Tuberculosis Control Section of the Philippine Health Bureau, during the ten-year period from 1933 to 1942, made 1,037,577 fluoroscopic and roentgenographic examinations with a prevalence rate of 6.53. The average was 103,757 examinations a year.

WAR DAMAGES AND CASUALTIES

The Pacific war has crippled the tuberculosis organization in the Philippines. There is no other health unit harder hit by the war than the Philippine Tuberculosis Society and its dependencies. Seven physicians on the staff died during the Japanese occupation. One was killed as a result of aerial bombing and the rest were either bayoneted to death or beheaded by the Japanese. Over 100 male patients and employees of the Quezon Institute were bayoneted to death in the last days of fighting during the liberation of Manila. Most of these patients were advanced cases and so weakened by disease and malnutrition that they could not walk alone.

Eleven dispensary clinics and four tuberculosis pavilions—two of the latter brand new—were damaged beyond repair; all their equipment and supplies lost or burned. The Quezon Institute proper, commandeered and occupied by the Japanese as a military hospital, was burned and greatly damaged by the Japanese before they evacuated it. What equipment and utilities remained after the conflagration was looted. Not only our research and clinical records since 1919 but ward, surgical, X-ray and laboratory equipment and supplies also perished during the fighting in the Walled City. Our medical and research libraries perished in the same fashion.

Damages sustained amount to at least two million dollars. Irreplaceable are our burnt medical books and literature, research records and X-ray and clinical records of patients dating from 1919.

The Tuberculosis Section of the Bureau of Health likewise lost all their mobile X-ray units—four in number.

PRESENT HANDICAPS

It has been sixteen months now since the Quezon Institute started operating again. The 80th U.S. Army Base hospital, which occupied the Quezon Institute for almost a year after liberation, made some repairs of the damaged buildings at the Quezon Institute, turned over their surplus to us in late December, 1945 on memorandum receipt. Some essential X-ray, surgical and clinical equipment is still lacking and some of us have grown rusty and turned into nervous wrecks with the war years, but most of the old crowd is back and new hands are being trained again. Present handicaps are plenty. Sanitary facilities are the

scarcest, for most of our plumbing and electric fixtures were lost. Foodstuffs, drugs and other commodities now are still scarce and expensive. Water mains remain unrepaired, hence there is water shortage in the Manila area. At the sanatorium it is very trying to have water only for three or four hours out of the twenty-four. That really poses a big problem in the face of some 1,200 sanatorium residents to take care of.

Our sincere thanks are due to the National Tuberculosis Association, which has aided the Philippine Tuberculosis Society in various ways. The NTA has given us an outright financial donation of \$5,000—when we were without any funds—Christmas seals, medical books, magazines, journals, educational posters, pamphlets and moving picture films, all of which not only have been of great practical and material help but also have bolstered our morale considerably. We desire to express our appreciation to many American doctors who have sent us relief supplies and medical literature.

At present we have been enabled to reopen five provincial dispensary clinics although only three of them have X-ray facilities.

The biggest problem of all is the inadequacy of funds for tuberculosis work. Even the governmental Tuberculosis Control Section, which is being aided directly by the USPHS, has the same financial problem. The USPHS has given us a \$5,000 donation for surgical equipment and two small X-ray units for which we are deeply grateful.

There are now two new miniature X-ray units under the Bureau of Health entity and 250 hospital beds for tuberculosis.

The present tuberculosis organization in the Philippines has a group of trained men and the spirit to combat tuberculosis. But it has only 1,200 beds now, where 70,000 are needed; not more than ten X-ray units, when at least twenty times that number are required. A program of expansion is on its way, depending upon available funds. The spirit is there—the spirit that made possible Bataan and Corregidor—even after the echoes of the most horrible war have just barely receded in the distance. Yet there is still “war” in this era of peace—the war against tuberculosis—as an already prostrate people succumbs at the rate of four deaths every hour, in the tuberculosis sector alone.

Notwithstanding which, the people of the Philippines go on serene and unperturbed, suffering in silence. The new Republic marches on with the Captain of the Men of Death stalking just behind. He carries a dark mantle in both hands, but life in the Philippines now—after the terrible misery and agony and devastation and cruelty of the war years—is comparatively sweet even if it is but a “tiny gleam of time between two eternities.”

TUBERCULOSIS IN AUSTRALIA

EMIL BOGEN¹

MORTALITY

Australia has had the lowest tuberculosis death rates of any country in the world, since data first became available (8). The apparently lower figures reported in New Zealand would be greatly increased by the inclusion of their Maoris, who form 6 per cent of her population but contribute more than a third of her tuberculosis deaths (12). Since aborigines in Australia constitute less than one per cent of the total population, it is unlikely that the indeterminable tuberculosis deaths among them would greatly affect the mortality rate from the disease in the entire continent. Inquiry into the causes for the low tuberculosis death rate in Australia appears desirable, then, as it might point the way for other countries to achieve similar desirable results. (See tables 1, 2 and 3.)

Tuberculosis is not a new or unknown disease in Australia. Consumption killed the first white man to be buried there, and a number of the convicts and other early settlers are known to have succumbed to the disease, but the fragmentary information available indicates that even in its early years tuberculosis was much less common in the colonies than in the mother country (3). The disease is said to have been on the increase before the discovery of the tubercle bacillus, but its death rate, even then, was less than half of that reported in most other countries (9).

From an annual death rate of more than 160 per 100,000 in 1882, tuberculosis has declined continually in Australia up to the beginning of this war, reaching a minimum of 33 per 100,000 in 1940, when that of the United States was 45. The decline stopped, and the rates even increased during the war, or in some states before the war began, but it is difficult at this time to evaluate the real significance of this contemporary trend. The tuberculosis death rates in the different states vary, that of Queensland being generally about one-third lower than that of Victoria, but most of the differences may be accounted for by differences in the age distribution of the populations; the general low level and steady decline are found in all (13). In every country tuberculosis causes much fewer deaths among children than in the old, and this disparity is especially marked in Australia, where the quarter of the population under 15 years of age contributed only 4 per cent of the tuberculosis deaths in 1940. Correction for this factor, by applying the age and sex specific tuberculosis death rates to the standard million population used by statisticians, still leaves the Australian situation better than that of other countries (7).

MORBIDITY

The prevalence of tuberculous infection in Australia, as revealed by tuberculin tests, has not been studied as extensively as that in the United States, but sample

¹ Olive View Sanatorium, Olive View, California.

test surveys in Queensland (6), New South Wales (1), Victoria (14) and South Australia (5) demonstrate that the percentage of positive reactions encountered at the ages tested is far below that usually reported in American and European countries. Analysis of extensive series of autopsies in South Australia (4) and in Queensland reveals a much lower frequency of tuberculous lesions, active or healed, than has been reported from other countries. This is particularly marked in the lower age groups. However small and unrepresentative some of the

TABLE 1
Tuberculosis mortality rates in Australia

1881-1885.....	164	1901-1905.....	113	1921-1925.....	62
1886-1890.....	161	1906-1910.....	92	1926-1930.....	56
1891-1895.....	140	1911-1915.....	77	1931-1935.....	45
1896-1900.....	122	1916-1920.....	71	1935-1940.....	38

TABLE 2
Pulmonary tuberculosis in twelve countries in two periods; and beds per annual deaths

	1931-1933	1940	BEDS PER TUBERCULOSIS DEATHS, 1934
Australia.....	122	33	0.9
New Zealand, white.....	94	34	1.9
Denmark.....	249	37	1.8
United States.....	249	43	1.3
England and Wales.....	194	53	1.0
Germany.....	348	62	0.7
Scotland.....	210	62	1.4
Italy.....	137	59	0.6
Switzerland.....	203	73	1.7
Japan.....	101	105	0.1
France.....	255	109	0.8
Finland.....	255	179	0.3

TABLE 3
Tuberculosis deaths and death rates in New Zealand, 1945, by race

Deaths, white 572	Maori 354	Total 926	Cases reported 6,772
Rate 37.2	Maori 369.1	Total 60.0	Beds in institutions 1,800

samples studied may have been, and however opinions may differ as to the cause of the lowered incidence found, their unanimity indicates that tuberculous infection in Australia is less wide-spread than in other countries.

Morbidity rates estimated from annual notifications of disease, from the central registries maintained in some places, or from special surveys tend to confirm the low incidence of tuberculosis indicated by mortality rates, autopsy examinations and tuberculin tests. The apparently high fatality ratio of 0.56 deaths per new case reported annually in 1940 suggests inadequate diagnosis or reporting. Some

doctors, even tuberculosis specialists, openly stated that they did not report cases, since it only led to undesirable publicity of the disease with loss of jobs, homes, etc. by the patient but never to anything being done for him by the health authorities, while others suggested that even the deaths from tuberculosis are understated because of social prejudice against the disease or fear of consequences by the physician certifying death in a patient who had not previously been reported to be tuberculous. In a few places central registries were incomplete, or contained duplicate and obsolete entries, and the importance of prompt notification and an up-to-date tuberculosis registry was insufficiently appreciated. (See table 4.)

CASE-FINDING

Case-finding activities suffer from the concealment of patients and contacts because of social opprobrium attached to tuberculosis, lack of coöperation of private physicians in looking for tuberculosis or notifying cases when found,

TABLE 4

Tuberculosis death rates, deaths, notifications of cases and institutional beds in Australian States

	QUEENSLAND	N.S.W.	SOUTH A.	WEST A.	TASMANIA	VICTORIA
Rate, 1940.....	28	35	37	42	43	43
Deaths, 1940.....	270	959	220	199	103	812
Notifications.....	248	1,907	276	263	248	911
Beds (1945).....	300	1,210	734	300	160	1,400

inadequate nursing force to make the necessary home visits and bring contacts in for examination, insufficient facilities for X-ray and other examinations, and refusal of contacts to report for examination and hesitancy in appealing for legal compulsion in such cases.

Fluorography with 35 mm. films, often with improvised equipment, is widely used in Australia. Candidates for the armed forces, workers at the Burnie paper mills, the Sydney transport workers, government employees in Victoria, and other large groups have been so examined, and private facilities have been made available for taking such films at low cost in various places, but there is still room for expansion of such efforts. The larger, 4 x 5 inch fluorograms are less popular than in the United States; stereoscopic films are infrequently encountered; and paper films and body section roentgenography are known only to a few men.

Sputum examination is intensively pursued by a number of men, who are using concentration and culture methods, fluorescence microscopy, and animal inoculation with typing of strains of tubercle bacilli obtained, but direct smears are more often used, and even these are too often neglected.

X-ray films of all admissions to general hospitals, to find early cases and to protect the other patients and the hospital staff from infection by patients with advanced disease, unknowingly admitted, are not yet utilized in Australia, though

repeated studies have emphasized the danger of the infection, especially to student nurses. The measures now in use in some places, tuberculin testing of nurses, refusal to accept nonreactors on tuberculosis wards, enforced vacation for those developing tuberculous infection even without other evidence of disease, need to be supplemented by case-finding efforts on all hospital admissions, and the use of adequate precautions in the care of all patients who are not known to be nontuberculous, as well as in the known consumptives.

State and voluntary outpatient clinics throughout Australia are unfortunately burdened with the care of tuberculous patients for whom there are no available hospital facilities; they are, therefore, unable to concentrate upon the case-finding and after-care programs which should be their chief concern. The ambulatory care of active cases of tuberculosis involves additional strain upon the patient who should be at rest, as well as the risk of spreading the infection among those with whom he comes in contact en route to the clinic or office consultation.

Preemployment and repeated fluorograms are taken in some industries with a silicosis hazard, such as mining, and other precautions are taken against silico-tuberculosis in their employees. Similar surveys have been attempted among factory workers, food handlers, and inmates of special hospitals, insane asylums, penal institutions, etc., where tuberculosis is unduly prevalent or dangerous, but much more remains to be done in this direction. Tuberculosis has been alleged to be frequent and fatal among the aborigines, who have little medical care, but individual cases observed indicate that they resist it much like white men, and no adequate statistical data are available (2). Tuberculosis in cattle and tubercle bacilli in market milk have been emphasized in Queensland, especially, and Australia is behind the United States both in the tuberculin testing of cattle and in the pasteurization of milk.

INSTITUTIONS

The most important single factor in the control of tuberculosis is the isolation and treatment of all active cases of the disease (10). Institutions for the care of the tuberculous were constructed in Australia at an early date, and increased especially during the first quarter of the twentieth century. Sanatorium construction lagged, and the number of beds actually used for the institutional care of the tuberculous even diminished in some places during the depression and second world war, but new facilities are being opened or contemplated in many places. Most Australian states have more than the old minimal requirement of one bed per annual death, but none yet even approaches the modern standard of three beds per death, and some fail to recognize the need for more adequate facilities.

Qualitatively as well as quantitatively, the tuberculosis institutions in Australia leave much to be desired. A few use the most modern forms of surgical treatment, pneumothorax, pneumonolysis or phrenephraphaxis, extrapleural pneumothorax, cavity suction drainage and thoracoplasty procedures, including bilateral collapse, and even lobectomy or pneumonectomy (11). But this is the exception, available to only a small fraction of the patients whom it might save. Many sanatoria afford only custodial care to the patients who do succeed in gain-

ing admission. Rest may be prescribed in some places but rarely is such a regimen rigorously followed. Injections of tuberculin, gold preparations, cadmium, mutton bird oil, and other treatments are used by enthusiasts in some places, but medical care often consists only of periodic visits by volunteer or honorary physicians, and even this is lacking in some places.

PREVENTION OF INFECTION

The exceptionally low tuberculosis death rates in Australia in early years may have been due, in part, to the long journey and hard life which deterred some who knew they were affected from attempting the trip, and hastened the death of others who might else have continued to infect their neighbors. There resulted a beneficial cycle, the low incidence of open cases of clinical tuberculosis making for a lowered incidence of the infection, and the lessened spread of the infection leading to a lowered incidence of clinical breakdown.

The spread of the infection may also have been retarded by the sparseness of the population, the diminished opportunities for effective contact between individuals living in small scattered buildings, the absence of slums and their congestion, the habits of open air living and the traditional English avoidance of the physical intimacies of more effusive peoples.

More important has been the extent to which patients with advanced tuberculous disease have been placed in general hospitals, almshouses and sanatoria, or otherwise taken from their family and other contacts at a time when they are expectorating great numbers of bacilli. This was done in Australia, as in England, more than in most other countries though it is still far from satisfactorily extensive. Part of the credit for the decline in the tuberculosis mortality rate in Australia may be given to even this inadequate degree of hospitalization and isolation of the vectors of the infection.

RESISTANCE TO DISEASE

The low tuberculosis mortality rates in Australia may not be ascribed to genetic factors, since the English people, who belong to the same racial stock, have so much higher rates. Development of a resistant strain by the survival of those who were not susceptible to tuberculosis cannot have occurred here where tuberculosis never killed the high proportions of the population it did elsewhere, though the failure of a resistant strain to have developed through the generations which have been decimated by the disease in Central Europe should have dissipated that notion long ago.

Nutritional factors raising resistance to tuberculosis may include the high total calorie intake, or the relatively high protein content of the average Australian diet. Qualitative dietary defects, especially lack of vitamins, of minerals such as calcium or fluoride, or of roughage, and excess of simple sugar and sweets, have been alleged as the cause of excessive dental caries in Australia. Leaders of Australian dentistry and medicine, as well as foreigners and laymen, have remarked upon the poor teeth observed there, though lack of proper dental hygiene and insufficient or unskilful dentistry are also blamed.

Despite the reputed hazard of the tropics for tuberculosis, and the high rates

reported in some tropical countries, the warm dry climate of Australia has also been given credit for its health. The bright sunshine was said to kill expectorated germs, and thus lessen air-borne infection, as well as to activate protective substances and lure people into the outdoor life.

More important, perhaps, though less tangible, is the generally slower tempo of the average Australian life. The short work-day and work-week, intermissions for tea in midmorning and midafternoon, as well as for regular meals, the frequent holidays and work stoppages for other causes, may evidence the strength of the labor movement, the tradition of industrial independence, the extensive system of pensions and aids, and the absence of abject poverty. The warm climate, well educated, widely traveled and leisure loving population and economic independence lead to habitual indolence, slowness of movement, taking it easy and coöperating instead of fighting nature and man, with an absence of the rush, anxiety and pressure felt in the hectic competition of the Northern cities. This type of existence, practically resembling a continued rest cure, such as might be advised for a patient with a quiescent tuberculous infection, may well be a determining factor in the low tuberculosis rates which have been found.

SUMMARY

Australia has consistently reported low tuberculosis death rates. The prevalence of tuberculous infection and morbidity are likewise low. Case-finding and institutional facilities are wide-spread but inadequate. Factors affecting the spread of the infection, and conditions affecting resistance to the disease are seen in the Australian way of living.

SUMARIO

Tuberculosis en Australia

Australia ha comunicado constantemente bajas cifras de mortalidad tuberculosa. La frecuencia de la infección y la morbilidad tuberculosas son igualmente bajas. El sistema de descubrimiento de casos y las instalaciones institucionales están difundidos, pero resultan inadecuados. Los factores que afectan la difusión de la infección y la resistencia a la misma se encuentran en las condiciones de la vida en Australia.

Acknowledgments

This rapid survey of tuberculosis in Australia is based mainly upon personal interviews in May and June, 1945 with scores of men and women interested in tuberculosis in most of the centres in the country, including physicians and surgeons, institutional, clinic, public health and private practitioners, lay employees, volunteer workers, and patients in clinics and sanatoria. Their kindly hospitality is greatly appreciated and whatever of value may reside in this study must be attributed to their aid, though errors of fact and interpretation must be blamed on the writer and on the haste with which the visits were made. Special thanks are due to the following for information which was utilized in this survey:

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STREPTOMYCIN-RESISTANT TUBERCLE BACILLI

Effects of Resistance on Therapeutic Results in Tuberculous Guinea Pigs¹

WILLIAM H. FELDMAN,² ALFRED G. KARLSON²
AND H. CORWIN HINSHAW²

Little precise information is available regarding the possible influence of drug resistance on the therapeutic effectiveness of streptomycin in infections produced by tubercle bacilli. It has been assumed that pathogenic bacteria in general which exhibit increased resistance against a chemotherapeutic agent *in vitro* will not likely be amenable to the therapeutic influence of the same drug *in vivo*. Clinical experience attests to the validity of this assumption.

With the increasing use of streptomycin in the treatment of clinical tuberculosis the problem of drug resistance has become exceedingly important as a limiting factor. After treatment for a few weeks to several months there is observed, in a considerable percentage of patients, a change in the *in vitro* resistance of the tubercle bacilli. Tubercle bacilli obtained from patients before treatment with streptomycin is started usually have a relatively low resistance (high sensitivity) to streptomycin *in vitro*. Conversely, tubercle bacilli observed in cultures obtained from the same patient after streptomycin has been administered for several weeks may have an *in vitro* resistance to streptomycin several thousand-fold greater than that at the onset of treatment. Under these circumstances it is generally believed that, when a streptomycin-resistant population of tubercle bacilli has largely or wholly replaced those that were sensitive to streptomycin in the first phase of the treatment, further administration of the drug usually is not warranted.

In order to determine if experimental tuberculosis infections produced by tubercle bacilli having a marked *in vitro* resistance to streptomycin would respond to streptomycin therapy the following studies were done.

METHODS

Two experiments were conducted concurrently: one with a normally sensitive culture of tubercle bacilli having an *in vitro* resistance to 0.31 microgram of streptomycin per milliliter of medium and one with a culture having an *in vitro* resistance to more than 2,000 micrograms of streptomycin per milliliter of medium. Both cultures were obtained from the same patient. The first mentioned or normally sensitive culture was isolated from a gastric lavage specimen obtained from the patient before any streptomycin was administered. The second culture was also obtained from a gastric lavage specimen

¹ A review of the evidence pertaining to the effectiveness of streptomycin in experimental tuberculosis induced by tubercle bacilli sensitive to streptomycin has been published previously (1). For a recent summary of the status of streptomycin in clinical tuberculosis the report by Hinshaw, Feldman and Pyle (2) may be consulted.

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after the same patient had received streptomycin for approximately four months.⁴ Each culture was used for subcutaneous inoculation of a separate group of 28 guinea pigs. The infective dose of tubercle bacilli for each animal was 0.1 mg. moist weight.

Twenty days after inoculation, 4 guinea pigs in each group were killed to determine the extent and character of the disease. The remaining animals in each group were then divided into 14 untreated controls and 10 to be treated with streptomycin. The daily dose of streptomycin was 6 mg. given in four equal doses at six-hour intervals.⁵ Treatment was continued until the 166th day after infection. During this period, treatment had been given for 146 days.

At the time of necropsy, tissues were obtained for subsequent histological study from the lungs, liver, spleen, tracheobronchial lymph nodes and from the area of inoculation in the subcutis. In addition, in most instances a portion of the spleen of the respective animals in the two groups that were treated and in the groups of untreated controls was cultured for tubercle bacilli. Positive cultures were later subjected to *in vitro* tests to determine resistance to streptomycin.

RESULTS

Relative survival times: The survival times of the treated and untreated animals constituting the two experiments are shown in figure 1. While there are some differences between the untreated controls in the two groups there is a marked distinction between the two groups of animals that were treated. At the end of the period of observation, 8 of the 10 animals inoculated with the streptomycin-sensitive culture and treated were living; only 2 had died. This was in marked contrast to the mortality among the guinea pigs infected with the resistant culture and treated, all but 2 of which were dead at the time the experiment was terminated.

Figure 1 indicates that the group that was treated after infection with the resistant culture did, as a whole, live somewhat longer than the untreated controls, also infected with the resistant culture.

The average survival times of the animals constituting the untreated controls in the two experiments were sufficiently dissimilar to justify brief mention. The first of the untreated animals inoculated with the streptomycin-sensitive culture died forty-four days after inoculation and the last animal in this group died 114 days after being infected. The average survival time for the group was 70.5 days. The first of the untreated controls inoculated with the streptomycin-resistant culture died thirty-two days after being infected; the last animal in this group died after 164 days. The average survival time for the 14 animals was 95.5 days. This represents an average of twenty-five days greater survival time for the group inoculated with the streptomycin-resistant culture than was true of the group infected with the streptomycin-sensitive culture. The standard error of this difference of survival time is \pm eleven days. Since the difference (twenty-

⁴ The daily dose of streptomycin was 2 g. given in four doses six hours apart. The method for determination of resistance to streptomycin *in vitro* has been described previously (3).

⁵ The streptomycin used in these studies was kindly supplied through the courtesy of the late Dr. D. F. Robertson, Merck & Co., Inc., Rahway, New Jersey.

five days) is more than twice its standard error, it may be considered statistically significant.⁶ This may indicate that the bacteria which are most resistant to streptomycin are less virulent than those which are sensitive to streptomycin. Obviously, definite conclusions regarding this are not warranted from the relatively meager data obtained. Additional observations will be necessary to establish definitely the influence of streptomycin resistance on the virulence of tubercle bacilli.

The evidence from this phase of the observations indicates definitely that,

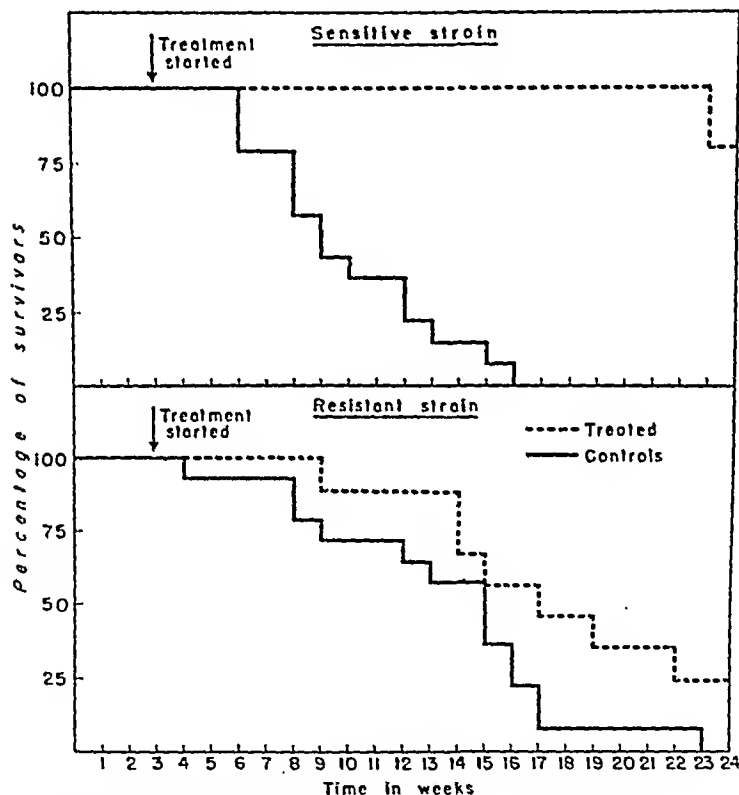


FIG. 1. Relative survival times of the four groups of animals in the two experiments.

while streptomycin may slow the tempo of the morbid processes caused by streptomycin-resistant tubercle bacilli, the ability of the drug to cope successfully with the infection caused by these bacteria is impressively diminished.⁷

Pathology: The extent and character of tuberculosis observed at necropsy in the 56 guinea pigs used in these studies are shown schematically in figures 2 and 3.

⁶ Statistical data kindly computed by Dr. Joseph Berkson, Division of Biometry and Medical Statistics, Mayo Clinic.

⁷ Miller (J.A.M.A., November 22, 1947, 155, 749) has reported that streptomycin may stimulate the growth of some, but not all, strains of streptomycin-resistant meningococci. We did not observe any similar phenomena with respect to the strain of streptomycin-resistant tubercle bacilli studied in our experiment.

It is of interest to note the wide-spread dissemination of the infection observed grossly in the 4 animals in each experiment that were killed twenty days after being inoculated. The infection had resulted in easily demonstrable lesions in the spleen, in the liver and, with the exception of one animal, in the lungs. From the point of view of relative virulence after twenty days, the two cultures were comparable.

As mentioned previously, the two groups of animals in each experiment that served as untreated controls had dissimilar average survival times (70.5 days and 95.5 days, respectively). However, the amount of tuberculosis recorded for the 14 animals in each group was essentially similar. The amount of disease in all of the animals was impressively severe and was presumed to have been the cause of death in each instance (figures 2 and 3).

Although the amount and severity of the disease were approximately the same in the untreated controls in each experiment, this was not true for the two groups of animals that had received treatment with streptomycin. The difference in the amount of tuberculosis in the two groups of treated animals was clearly evident at the time of necropsy (figures 2 and 3). Seven of the 10 animals inoculated with the streptomycin-sensitive culture were without gross signs of tuberculosis in the organs of predilection (spleen, liver and lungs), whereas all 10 animals inoculated with the streptomycin-resistant culture were severely affected. In fact, the degree of involvement among the treated animals in this experiment was comparable to that observed in the untreated controls (figure 4).

Tissues from all of the animals in both experiments were examined microscopically. This phase of the study is summarized in part in table 1. From these data the amount of tuberculosis in the two groups of untreated controls and in the group inoculated with the streptomycin-resistant culture and treated is essentially the same. This is especially impressive when these results are contrasted with the amount of tuberculosis observed in the group inoculated with the streptomycin-sensitive culture and treated. In this instance the average index of infection (based on an arbitrary maximal figure of 100) was 13.2, while the figures for the other three groups were 95, 90.5 and 91, respectively.*

Microscopically there were no unusual histopathological features observed in the tissues from the animals inoculated with the streptomycin-resistant cultures prior to treatment with streptomycin. The disease in this group was similar in every respect to that observed in the untreated controls. The pathological process was that of an actively destructive, apparently unrestrained tuberculosis infection in which any deterrent effect of the treatment was not detected (figures 5 and 6).

The microscopic examination of tissues from the animals in the treated group that had been inoculated with the streptomycin-sensitive culture revealed an entirely different situation. In 2 of the 10 animals no lesions of tuberculosis were found in the parenchymal organs of predilection. In 5 others the disease was limited to small calcified nodules in the spleen (figure 7). As was mentioned previously, 3 of the 10 animals in this group had extensive lesions of active

* The scheme used to determine the index of infection has been described previously (4).

tuberculosis. In these, the lungs and spleen especially were involved. It was of interest to observe that the liver in each of the 3 animals in which the disease was

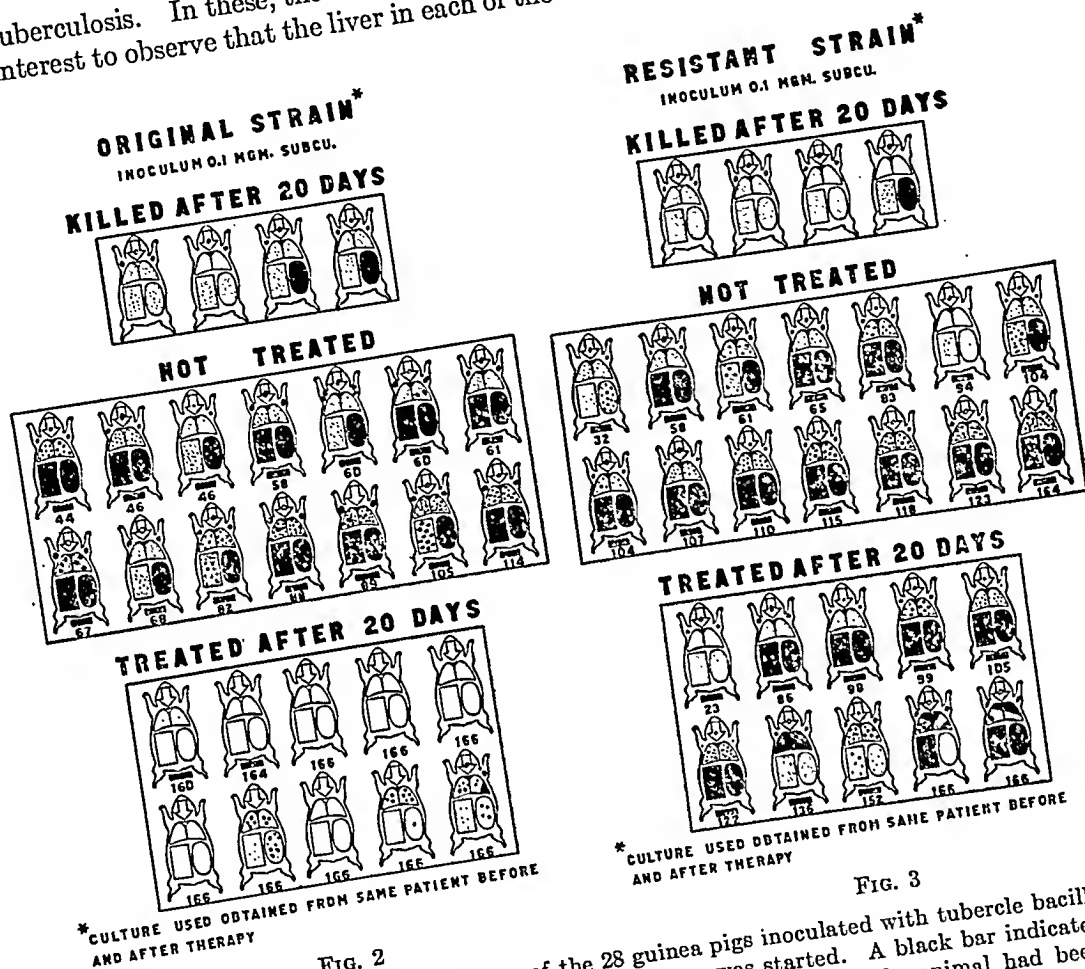


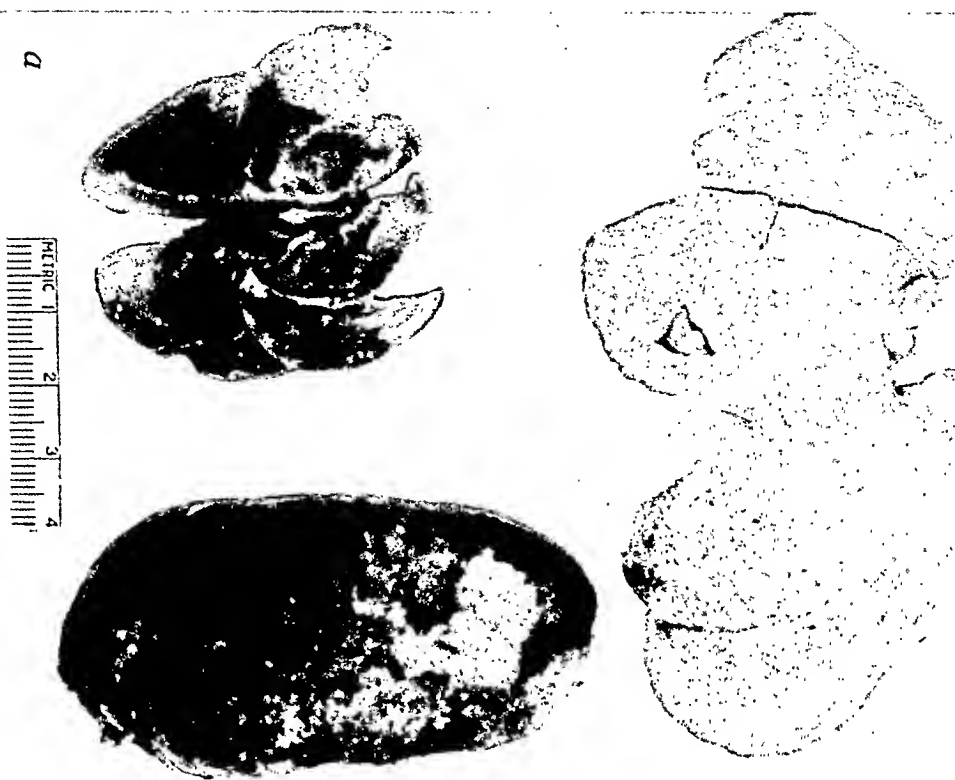
FIG. 2

FIG. 2. Schematic representation of the 28 guinea pigs inoculated with tubercle bacilli isolated from a patient before streptomycin therapy was started. A black bar indicates that the animal died; the numeral represents the number of days the animal had been infected. Note the extent of the disease before treatment was started (top row). The difference in the amount of tuberculosis between the untreated animals and those that received streptomycin is striking.

FIG. 3. Schematic representation of the 28 guinea pigs inoculated with tubercle bacilli isolated from the patient after months of treatment. (The culture was resistant *in vitro* to more than 2,000 micrograms of streptomycin per milliliter of medium.) A black bar indicates that the animal died; the numeral represents the number of days the animal had been infected. Note that the amounts of tuberculosis in the untreated and the treated groups are comparable, indicating little if any effect of treatment.

active in the spleen and lungs was practically free of lesions. Another interesting observation pertaining to the disease in the 3 animals mentioned was the relative "age" of the lesions as judged by their microscopic appearance. Compared with

FIG. 3



b



Fig. 4. *a*) Lungs, liver and spleen of an untreated guinea pig inoculated 104 days before death with a streptomycin-resistant culture of tubercle bacilli. Severe tuberculous involvement of the liver and spleen. Minimal involvement of the lungs. *b*) Lungs, liver and spleen of a guinea pig inoculated ninety-nine days before death with a streptomycin-resistant culture of tubercle bacilli and treated with streptomycin the last seventy-nine days of life. The disease is severe in each of the three organs.

the appearance of the lesions in the untreated control animals in which the infection was of comparable duration, the active lesions in the animals that re-

TABLE 1

*Average severity of tuberculosis in different organs expressed numerically**

CULTURE	GROUP	ANIMALS	SPLEEN (MAX. 35)	LUNGS (MAX. 30)	LIVER (MAX. 25)	SITE OF IN- OCULATION (MAX. 10)	AVERAGE INDEX OF INFECTION (MAX. 100)
Sensitive to streptomycin	Controls	14	35	25	25	10	95
	Treated	10	3	7	0.27	3	13.27
Resistant to streptomycin	Controls	14	32.8	25.7	22	10	90.5
	Treated	9†	31	29	21	10	91

* Data based on the histopathological characteristics of the tissues indicated.

† Of the 10 animals in this group originally, one died prematurely.

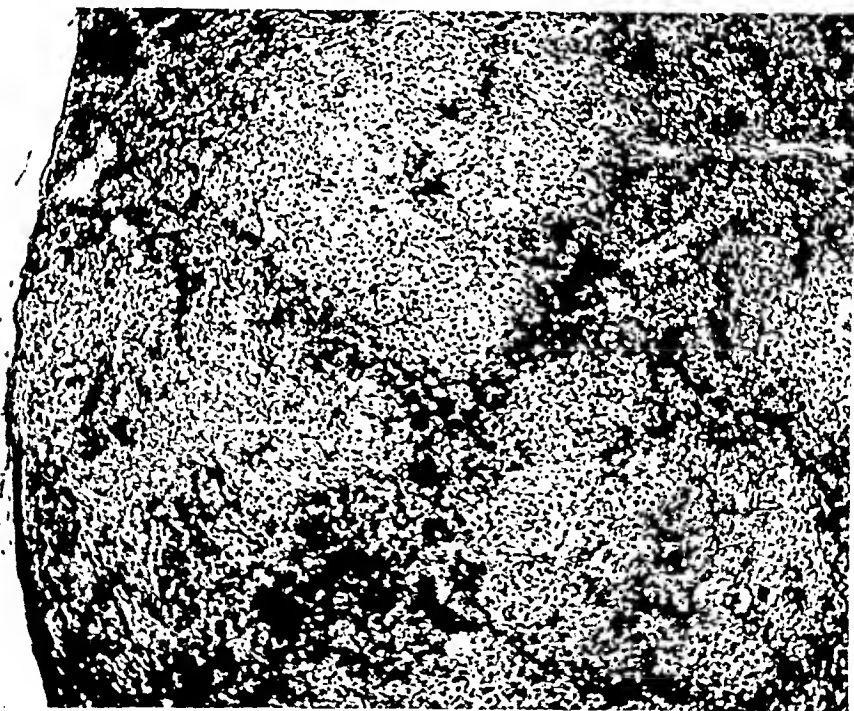


FIG. 5. Spleen of treated guinea pig infected with streptomycin-resistant culture of tubercle bacilli. Animal died sixty-six days after inoculation and had been treated for forty-six days. Numerous active tuberculous foci. ($\times 70$)

ceived treatment appeared to be of more recent origin. Furthermore, in some situations actively progressive lesions appeared in areas adjacent to lesions that

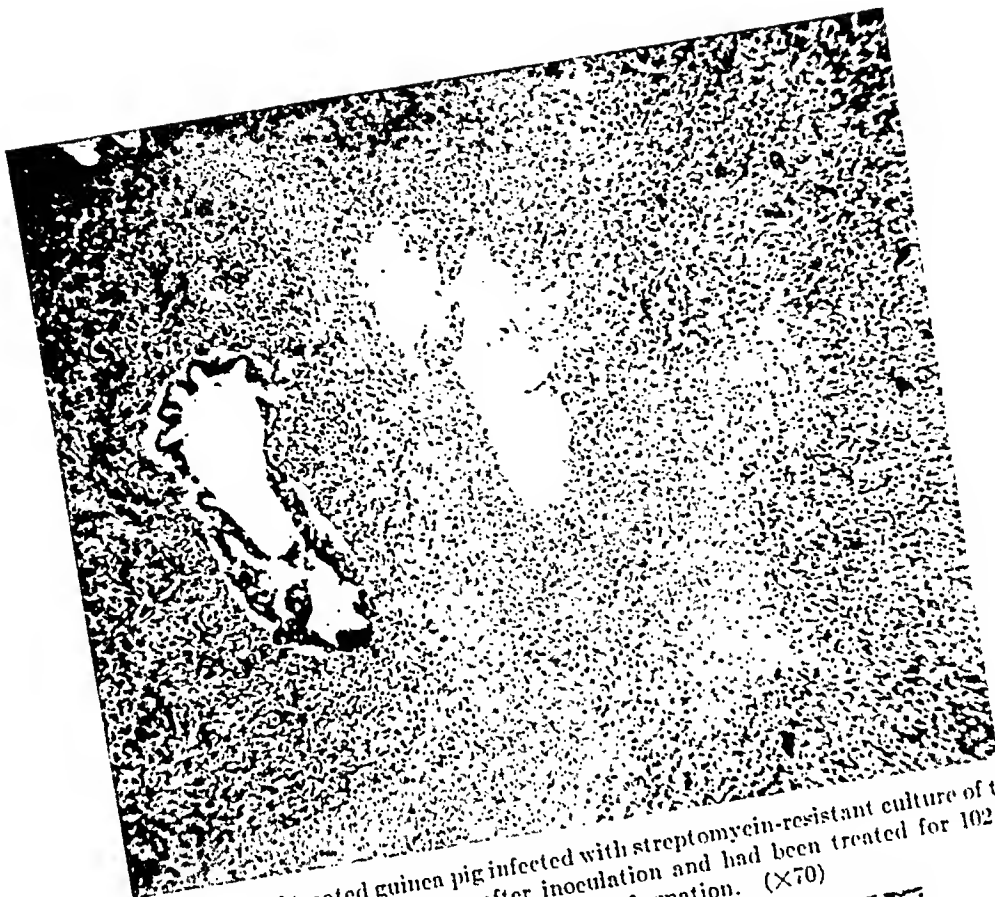


FIG. 6. Lung of treated guinea pig infected with streptomycin-resistant culture of tubercle bacilli. Animal died 122 days after inoculation and had been treated for 102 days. Destructive tuberculous lesion with early cavity formation. ($\times 70$)

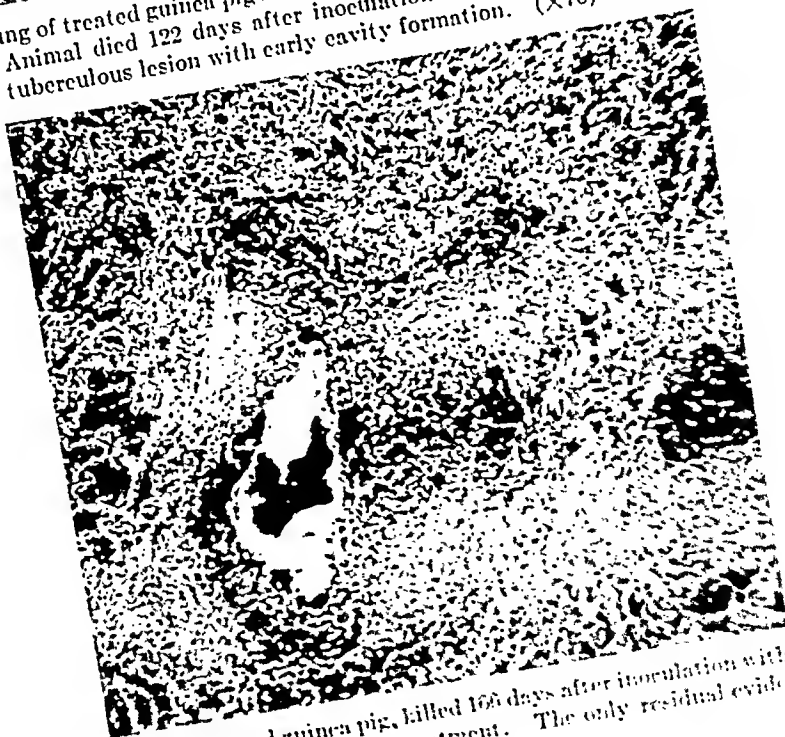


FIG. 7. Spleen of treated guinea pig, killed 166 days after inoculation with streptomycin-sensitive culture and after 146 days of treatment. The only residual evidence of tuberculous infection was a small calcified nodule. ($\times 70$)

were calcified and apparently inactive (figure 8). A possible explanation for this unique combination of morbid changes is to be had from the results of the study of the cultures obtained from the affected tissues. These will be referred to later in this report.



FIG. 8. Spleen of guinea pig, inoculated with streptomycin-sensitive culture, which was killed 166 days after inoculation and 146 days after beginning of treatment. Tubercle bacilli having a resistance to streptomycin greater than 3,000 micrograms per milliliter were isolated from a portion of this spleen. *a*) Small calcified lesions, apparently inactive. ($\times 70$) *b*) Region of active tuberculosis adjacent to calcified nodule shown in *a*. The active process appears to be of more recent origin than the lesions which are calcified. ($\times 70$)

Residual infection: Cultures of acid-fast bacilli, presumably tubercle bacilli, were isolated from the tissue suspensions prepared from each of the spleens of the treated animals inoculated with the streptomycin-resistant culture. From the spleens of the treated guinea pigs inoculated with the streptomycin-sensitive culture, attempts to isolate acid-fast bacilli failed in 2 instances and were successful in 8.⁹

⁹ These results are consistent with previous experience (5) and emphasize again the suppressive rather than the sterilizing effect of streptomycin on tubercle bacilli *in vivo*.

Streptomycin resistance of cultures isolated: The splenic cultures obtained in both experiments from the animals that had been treated with streptomycin were subjected to tests *in vitro* to determine if residence in the animals had altered appreciably the resistance to streptomycin determined originally for the two cultures constituting the infective inocula.

The results of this portion of the study indicate that (1) the cultures obtained from the specimens of both groups of the guinea pigs, treated and controls, inoculated with the streptomycin-resistant culture had in all instances the same relative degree of resistance as the original culture; (2) of the 8 cultures obtained from the spleens of the animals inoculated with the streptomycin-sensitive culture (and treated with streptomycin), 5 had a resistance to streptomycin respectively as follows: 0.31, 0.31, 0.15, 0.08 and 0.15 microgram per milliliter of medium. Thus there was no evidence that in these 5 animals resistance to streptomycin had been altered as a consequence of treatment. Cultures were obtained from 10 of the untreated controls inoculated with the sensitive culture and all had the same rate of sensitivity to streptomycin as the original culture.

It will be recalled that 3 of the treated animals in the group inoculated with the sensitive culture had considerable tuberculosis at the time of necropsy. Microscopically most of the lesions appeared to be of recent origin and in some instances active lesions of recent origin appeared in areas where nonactive or arrested lesions also occurred (figure 8). The streptomycin resistance of cultures obtained from these 3 animals was strikingly different from that of the other cultures obtained from animals in the same group mentioned previously. Whereas the cultures obtained from the animals in which the disease had been rather successfully suppressed had a very low resistance to streptomycin, the cultures isolated from the 3 animals in which the disease was not under control had a very high resistance to the drug. The resistances of the 3 cultures were more than 2,000, more than 3,000 and more than 2,000 micrograms, respectively, of streptomycin per milliliter of medium.

These observations on the occurrence of highly streptomycin-resistant tubercle bacilli in animals inoculated with tubercle bacilli of low resistance explain the failure of streptomycin therapy to exert a continuing successful restraining influence on the infection. We are not aware of any previous reports which describe the development of resistant strains of tubercle bacilli in guinea pigs as a result of treatment.

It would appear that, during the earlier phase of treatment when the vast majority of the infective organisms were highly sensitive to the suppressive effects of the drug, the lesions that existed when treatment was started were eventually resolved or fibrosed and calcified. This was evident from the finding of lesions of different "morphological age" in the same organ.

COMMENT

These experiments have provided definite evidence that in the guinea pig streptomycin is not therapeutically effective if the tuberculous disease is induced

by a highly resistant strain of tubercle bacilli.¹⁰ The possible clinical implications of this observation are suggested. However, one must recognize that in clinical tuberculosis the great majority of strains of *Mycobacterium tuberculosis* have relatively low resistance to streptomycin at the time when treatment is started. The expected therapeutic benefits of the drug will in some types of cases be accomplished before the streptomycin-resistant tubercle bacilli predominate. This may occur after treatment for several weeks or even several months.

During the period of treatment when tubercle bacilli of low resistance constitute most of the bacterial population, the suppression of the organisms—and perhaps the killing of some—enables the natural defenses of the patient to become, in most cases, effectively operative. As a consequence there is set in motion the complex mechanisms of resistance and repair which were latent or suppressed as long as the large majority of the infective bacteria were undisturbed in their natural progression. Once activated as a result of the action of streptomycin on the sensitive bacteria, the forces of repair seem, in most instances, to continue effectively operative. After streptomycin therapy is discontinued, even though highly streptomycin-resistant tubercle bacilli can, for a time at least, be isolated, the forces of resistance and repair are often expressed in the continued betterment of the clinical course of the disease.

The case of pulmonary tuberculosis from which the two cultures used in our two experiments were obtained is illustrative of this course of events. Streptomycin therapy of this patient was discontinued on January 1, 1946, at which time the tubercle bacilli obtained from gastric lavage specimens were highly resistant to streptomycin *in vitro* and *in vivo*. Specimens of gastric lavage were used to inoculate guinea pigs in March, April, May, June, July, August, September and November, 1946, and in no instances were signs of tuberculosis observed when the animals were killed for necropsy eight weeks after being inoculated. Consistent with these observations was the clinical status of the patient. She continued to improve and apparently the disease finally became stabilized. At the present time, sixteen months after treatment with streptomycin was discontinued, there has been no detectable reactivation of the disease.¹¹

SUMMARY AND CONCLUSIONS

A study was done to determine if infections produced by tubercle bacilli having a marked *in vitro* resistance to streptomycin would respond to streptomycin therapy. Tubercle bacilli with a normal sensitivity to streptomycin were ob-

¹⁰ Essentially similar results have been reported by Youmans (6) in experimental tuberculosis of mice induced by streptomycin-resistant strains of tubercle bacilli.

¹¹ Since this paper was written another gastric lavage specimen was obtained (April 9, 1947) and used to inoculate guinea pigs. Eight weeks later, when the animals were killed for necropsy, no signs of tuberculous infection were observed. A more recent report (December 20, 1947) indicates that the suppression of the disease in the patient has continued, approximately two years after streptomycin therapy was discontinued.

tained from a patient before treatment with streptomycin was started. A culture, resistant to streptomycin *in vitro*, was obtained from the same patient after treatment for four months with streptomycin. Two experiments were done concurrently. In one, guinea pigs were infected with the sensitive culture and in the other experiment a similar group of guinea pigs were infected with the resistant culture. Twenty days after inoculation, treatment of 10 animals in each experiment with streptomycin was begun. Treatment was continued daily until all of the untreated controls had died (approximately twenty-three weeks).

The results showed that the disease in the animals infected with the streptomycin-sensitive culture responded favorably to treatment. However, in 3 of the 10 animals, active lesions of recent origin were present. Streptomycin-resistant tubercle bacilli were obtained from each of these 3 animals. The disease in the animals infected with the streptomycin-resistant culture failed to yield to treatment. In this instance the amount and character of the tuberculosis in the untreated controls and in the treated group were comparable.

It is concluded that infections in guinea pigs induced by tubercle bacilli resistant *in vitro* to streptomycin are refractory to treatment with this antibiotic.

SUMARIO Y CONCLUSIONES

Bacilos Tuberculosos Estreptomicinorresistentes

En este estudio tratóse de determinar si las infecciones producidas por bacilos tuberculosos dotados de notable resistencia a la estreptomicina *in vitro*, responden a la estreptomicinoterapia. Antes de iniciar el tratamiento con estreptomicina, obtuviéronse de un enfermo bacilos tuberculosos que mostraban resistencia normal a la estreptomicina. Obtúvose, del mismo enfermo, después de ser tratado por cuatro meses con estreptomicina, un cultivo resistente *in vitro* a la droga. Efectuáronse dos experimentos concurrentemente. En uno se infectó a cobayos con el cultivo sensible y en el otro a un grupo semejante con el cultivo resistente. A los 20 días de la inoculación comenzó el tratamiento con estreptomicina de 10 animales en cada grupo, continuándose a diario hasta la muerte de todos los testigos no tratados (unas 23 semanas).

El resultado demostró que la enfermedad en los animales infectados con el cultivo sensible a la estreptomicina, respondió favorablemente al tratamiento, aunque en 3 de los 10 animales había presentes lesiones activas de origen reciente. De estos tres animales obtuviéronse bacilos tuberculosos estreptomicinorresistentes. En los animales infectados con el cultivo estreptomicinorresistente la enfermedad no cedió al tratamiento. La proporción y naturaleza de la tuberculosis en los testigos y en el grupo tratado eran comparables.

Dedúcese que las infecciones evocadas en los cobayos por bacilos tuberculosos resistentes *in vitro* a la estreptomicina son refractarias al tratamiento con este antibiótico.

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BOOKS

ELI H. RUBIN: *Diseases of the Chest. With Emphasis on X-ray Diagnosis.* Pp. 685, with 355 illustrations (24 plates in color), W. B. Saunders Company, Philadelphia and London, 1947, cloth, \$12.00.

By CHESLEY BUSH

Popularity of the study of diseases of the chest has been increasing for the past few years. Rapid strides have been made by thoracic surgery giving more light to the anatomy and physiology of the chest, in addition to technical operative procedures. The advent of a new volume in this field bears witness to this.

Doctor Rubin's book is by far the best exhibition of good format and good printing that has come to our attention lately. The illustrations, many of which are in color, are exceptionally clear and well done. They alone make the book of permanent reference value.

The author states that he desires to approach this subject mainly from the viewpoint of roentgenology and he has accomplished his purpose very skilfully. In addition he has also presented his subject in a clear, practical and concise form "without neglecting basic aspects." The two-column construction of the page has given more space for his subject than would be possible otherwise. The page is a delight to the eye as a specimen of the printer's art.

The structure of the book should be praised. It is logical, complete and clear. Each subject is introduced completely with histogenesis and pathology, and certain illustrative case studies are included. We are glad to see the heart becoming recognized as a part of the chest. Doctor Rubin has included it in its relations to other chest conditions, and should be given much credit for doing so.

The subject of tuberculosis is well considered and it is to be noted that all modern methods of treatment are included, the fundamentals as well as the technical procedures. This is the first time that pneumoperitoneum as a therapeutic procedure for pulmonary tuberculosis has been included in a text-book. It is also to be noted that histoplasmosis is fully discussed in the light of recent work, providing an explanation for the tuberculin-negative person with intrathoracic calcifications.

Certainly many specialists dealing with diseases of the chest may not agree with all the statements made. There are probably few fields of medicine where wider divergences in policies and procedures exist than in the treatment of pulmonary tuberculosis. This is noticeable in various parts of the country—and in various clinics. Doctor Rubin treats the fundamentals well—but some might criticize the use of pneumothorax in tuberculous pneumonias, and others would say that the complications of artificial pneumothorax are not sufficiently emphasized. Many of us believe that, as a general rule, more than one stage of pneumonolysis should be avoided, but that continuation of a pneumothorax in which adhesions are not cut is poor treatment.

Doctor Rubin should be congratulated for the space and emphasis he has placed

on post-surgical care. The section on emergencies of the chest is also a commendable thought. The bibliographical references are carefully and critically selected; the index appears to be well prepared.

The conclusion of this reviewer is that we have here a very valuable addition to the field of medical texts, and that this volume should be a part of the medical library of those interested.

ARCHIBALD REYNOLDS JUDD: *Diseases of the Chest. Diagnosis and Treatment.* Pp. xii + 608, with 140 illustrations, Philadelphia, F. A. Davis Company—Publishers, 1947, cloth, \$9.00.

By CHESLEY BUSH

The author states that he desires to produce "a brief manual for the general practitioner." On first inspection the book appears of considerable size and weight for a brief manual, but the paper is very heavy and the type is very large—so brevity is indeed attained, possibly more than desirable for the general practitioner. There is also an effort at simplification so that he who runs may read.

The structure of the book is not beyond criticism. There is no logical sequence and subjects are discussed under headings where one does not expect to find them. Factors of resistance to tuberculosis, classification of pulmonary tuberculosis and other matters are included under the heading *Pneumothorax*. In fact, the two hundred and more pages devoted to pulmonary tuberculosis are largely occupied by expositions of technical procedures and one page is devoted to the fundamental problem of rest. The use of certain procedures and their techniques change very rapidly in our present world of progress—and consequently this book will not last as an authoritative guide. In fact, we have here an evidence that it is difficult to keep texts up-to-date even on publication. Pneumoperitoneum is not mentioned as a therapeutic procedure in the treatment of pulmonary tuberculosis, and yet it is being more widely used day by day in this country. Histoplasmosis is not found in the index although it is important in the diagnosis of pulmonary disease, as well as an entity in itself.

Tracheobronchial tuberculosis is considered as a separate disease and not as a part of pulmonary disease. And yet if any fact has impressed itself on those dealing with pulmonary tuberculosis these days, it is that the bronchial factor is present in most pulmonary lesions, and that bronchopulmonary tuberculosis is probably a better descriptive term than plain pulmonary tuberculosis. Also pleurisy with effusion is treated under diseases of the pleura—but its intimate connection with tuberculosis and pulmonary disease is hardly emphasized.

The book appears to be slanted all the way toward a surgical viewpoint. This would be satisfactory if the medical aspects were also included. Pneumonolysis occupies twenty-eight pages versus one page on rest, as an example.

In conclusion, the reviewer doubts that this book meets the requirements of the general practitioner.

LEWIS J. MOORMAN: *The American Sanatorium Association. A Brief Historical Sketch. Historical Series Number 3, pp. 72, National Tuberculosis Association, New York, 1947, paper.*

By SIDNEY J. SHIPMAN

This booklet is a valuable reference manual for those interested in the origin and background of the American Sanatorium Association, the predecessor of the American Trudeau Society. For those acquainted with the early years of the American Sanatorium Association, the historical notes will bring back a host of memories and the names of many friends who have gone before. A list of programs and committee activities which follows might be rather dull reading were it not for the fact that these activities portray vividly the changing trends of thought in the minds of those workers most interested in the management of tuberculosis during the years covered by the booklet. For example, the early controversy regarding heliotherapy in tuberculosis was a subject of many papers prior to the crystallization of thought. The early controversies regarding activity are described, a subject that bids fair to be again in the foreground of discussion because new methods have shown that it is still—or again—a moot topic. The steps that led to the formation of the American Trudeau Society are described.

Doctor Moorman's lucid and concise style contributes much to the interest in this historical development which will become increasingly valuable for reference as time goes on.

Industry, Tuberculosis, Silicosis and Compensation. A Symposium. Prepared by the Committee on Tuberculosis in Industry of the National Tuberculosis Association and American Trudeau Society. Leroy U. Gardner, Editor. Published by National Tuberculosis Association, New York, 1945. Contributors: Paul Bamberger, Leopold Brahdry, Leroy U. Gardner, David Gould, L. E. Hamlin, Herman E. Hilleboe, B. E. Kuechle, A. J. Lanza, Ada Chree Reid, O. A. Sander, W. P. Shepard, C. D. Selby, George Wright. Pp. 126, cloth.

By HARRIET L. HARDY

Having just attended the Saranac Symposium of 1947, the first since the war, this reviewer of *Industry, Tuberculosis, Silicosis and Compensation*, a National Tuberculosis Association monograph, understands what the late Doctor Gardner and the Association had in mind in its preparation. The dissemination of accurate knowledge of pulmonary disease in industry to those who need such material is not easy because of widely divergent training and point of view, as represented by family physician, plant physician, compensation lawyer, plant manager and safety engineer, to enumerate a few specialists concerned. This group of papers for the most part succeeds in giving the necessary data to members of different disciplines in utilizable form.

Being a physician, this reader was most interested in the chapters on the diagnosis of the pneumoconioses prepared by Dr. Hamlin, Dr. Sander and Dr. Gardner. The family physician is so often puzzled by X-ray reports including reference to a pneumoconiosis in the differential diagnosis, that he would do well to own this monograph for reference. The practitioner will be helped, in general, by the chapters on the treatment of silicosis. What is said is thoroughly safe and sound. Because of the current interest, one would like to know a bit more about present practice, though experimental, with aluminum as prophylaxis and therapy in humans.¹ Public health authorities and plant physicians will be gratified by the support of their efforts in promoting chest X-ray surveys provided in Part I.

Since so much was said about the engineering control of dust hazards, it might have helped the medical men and the owners of small plants, who do not have full-time engineering help, to have had a not too technical chapter on this subject.

Doubtless because the subject itself is so complex, this reviewer found Part III on compensation the least satisfactory section of the book. It is excellent to raise questions and point out responsibilities, but since the intent of the volume seemed to be primarily informative, the compensation section might have been handled differently. Doctor Brahdý has too much confidence in medical skills alone. It very often happens that a physician cannot make a correct diagnosis of occupational etiology in a given case of disease without help from a properly qualified chemist or an industrial hygiene engineer or both. The real problem here is that many physicians are not aware of this lack and do not know where to look for correct data.

Mr. Kuechle remarks, "Many times even the employer dealing with new chemicals or new combinations of chemicals is unaware of potential hazards to the health of his workers." Is it not reasonable to suggest that the employer is responsible for making certain, before he uses potentially hazardous materials, that he has all available data on the action and prevention of toxic effects, if they exist, of such material?

Industry, Tuberculosis, Silicosis and Compensation should be widely distributed and used to increase the usefulness of the present important chest X-ray surveying being done in industry throughout the country.

MANUEL TAPIA: *Formas Anatomoclinicas, Diagnóstico y Tratamiento de la Tuberculosis Pulmonar. Tomo II. Pp. 538, with 439 illustrations, Livraria Luso-Espanhola, Lda., Rua Nova do Almada, Lisboa—Barcelona, 1946, paper.*

By WILHELM SWIENTY

In the opening chapters of this second volume of his standard work, Doctor Tapia continues the detailed description of all those types of reinfection tuber-

¹ This topic is discussed in a paper by Dr. John W. Berry, soon to be published in the REVIEW, accompanied by an Editorial on the same topic by Dr. Anthony J. Lanza. [Editor]

culosis which have not been dealt with in the first volume: fibro-caseous and caseous tuberculosis, the cavity complex, atelectasis and pleural tuberculosis.

It is Doctor Tapia's contention that the definition of a cavity should be revised. Every tuberculosis starts with caseation. The defensive body reactions decide whether the further development of the disease is in the direction of an exudative-progressive or a fibrous-retrogressive process. The tissue destruction in tuberculosis is essentially cavitary. From an anatomical point of view, practically every case of tuberculosis shows destructive foci of various sizes which often cannot be visualized in the conventional X-ray film nor even in tomograms. A great number of cases with small cavities have no clinical symptoms and remain undetected during life. For this reason, the old concept which identified cavities with a far advanced process should be abandoned.

In Doctor Tapia's classification, pleural tuberculosis is regarded as a special manifestation of tuberculosis; he believes that primary pleural tuberculosis is much more common than most authors think. For the development of pleurisy, the existence of a primary focus and a particular allergic condition are necessary. If these two factors are not present, a local inflammation of the serous membranes may result with later formation of adhesions. This is in contradiction to the generally accepted opinion that the exudate is the primary step for the formation of adhesions which appear in the region of a peripheral parenchymal lesion with involvement of the pleura. Doctor Tapia's assertion that pleural obliteration and adhesions may form without pleural exudate is hard to follow.

The second half of the book is devoted to the clinical and radiological diagnosis of tuberculosis and the differential diagnosis with other pulmonary diseases. The diagnostic X-ray techniques and methods are described in detail, as are the bacteriological procedures. A critical evaluation of the sero-diagnostic tests is given. Although no one method has been satisfactory as yet, further investigation and development of the flocculation and the complement fixation tests should be encouraged, because such a specific test for tuberculosis would make early diagnosis possible in more cases than with the standard examinations of to-day.

The observations about tuberculin reactions in nontuberculous diseases are of great interest. In acute infections with or without involvement of the respiratory tract, previously positive tuberculin reactions disappeared during the acute phase of the disease in almost all of the many cases observed by the author. They reappeared slowly and progressively during convalescence. Only in miliary tuberculosis and in the terminal stages of other forms of tuberculosis does allergy wane. In Doctor Tapia's opinion, this transitory disappearance of tuberculin allergy in infections of undetermined etiology is proof of their nontuberculous nature.

The importance of Arneth's index and of the sedimentation rate is discussed. The increase of plasma proteins is a sign of the response of the defense mechanism to the infection. New investigations may, by using the protein-globulin ratio, establish a reliable index for the prognosis of pulmonary tuberculosis.

Unusually clear X-ray positives illustrate the many case histories. Unfor-

tunately, few tomograms are used; and bronchography has been neglected throughout the entire volume, even in the chapters on bronchiectases and bronchial carcinoma. The frequent misspelling of names, the many typographical errors, the lack of a bibliographical index and the author's frequent use of his own very personal terminology ("granulitis" for miliary tuberculosis etc.) are annoying. As in the first volume, the modern Anglo-American literature is only occasionally referred to. With these exceptions, the book is recommended reading for the specialist.

MANUEL TAPIA, LUIS QUINTELA AND ANSELMO FERRAZ DE CARVALHO: *El neumotorax extrapleural*. Pp. 246, with 117 illustrations, *Livraria Luso-Espanhola, Lda., Rua Nova do Almada, 86 a 90, Lisboa—Barcelona, 1947, board.*

By A. A. MOLL

Extrapleural pneumothorax has been one of the most controversial procedures in the surgical treatment of tuberculosis. This monograph explains its foundations, its technique and its indications as well as its complications, deficiencies and disadvantages. The need of early diagnosis and the different results secured by various surgeons are pointed out. Tuffier is given credit for his pioneer work in pulmonary surgery, beginning with his pleuroparietal *decollement*—the forerunner of extrapleural pneumothorax—in 1891 and, after a series of changes including plombage, going back, in 1926, to extrapleural pneumothorax. Typical well illustrated case histories are reported to demonstrate the points emphasized. The literature cited is ample and representative, including a number of American papers, most of them published in the REVIEW, and a few from Latin America. The series of cases treated by the authors, with a follow-up period of at least six months, numbers 73; with good results in 67.2 per cent, doubtful in 8.2 per cent, and failures in 24.6 per cent. This compares to a grand total of 60 per cent of successes with extrapleural pneumothorax in the literature. The rate of successes went up to 73 per cent in 52 uncomplicated cases and 92.5 per cent in 27 "ideal" cases, but it decreased to 52 per cent in 25 patients in whom indications were liberalized. Results were somewhat better with oleothorax (78.3 per cent in 23 cases) than with pneumothorax (68.9 per cent in 29 cases). Negative findings with tomography and guinea pig inoculation are considered the measures of success. Corrected operative fatality did not exceed 2.7 per cent in the series. The so-called medical extrapleural pneumothorax sponsored by Rotta is not encouraged. Its use, however, by Medici and Sampietro in Argentina for sectioning otherwise noncuttable pleural adhesions is praised. This book is a conscientious and fair appraisal of a method in dispute by experts familiar with practically every phase of the subject.

R. O. DRABKINA: *Allergy in Tuberculosis. State Institute for Scientific Research in Tuberculosis at Kiev, 1940*

By MAX B. LURIE

This is a comprehensive review of the world literature on allergy and immunity in tuberculosis down to 1938. It also includes an original investigation on the nature and rôle of heteroallergy in tuberculosis. It presents additional evidence for the view that tuberculosis enhances the physiological activity of the reticulo-endothelial system not only against the tubercle bacillus, but also against a variety of unrelated bacteria, such as colon bacilli, streptococci and staphylococci. This is evidenced not only by an increment in the phagocytic activity of these cells for these microorganisms, as demonstrated by other workers, but also by the greater capacity of tuberculous animals to remove these microorganisms from the circulation. This increased reactivity of the reticulo-endothelial system also explains the enhanced resistance of tuberculous animals against cholera, anthrax etc. In the same category is included the observation of the greater capacity of tuberculous animals to produce nonspecific antibodies. The increased toxicity of colon bacilli for tuberculous animals is ascribed to the same mechanism; for, the activated mesenchyme of the allergic animal may release more endotoxin from colon bacilli in a given time than that of a normal animal. However, this increased sensitivity of the tuberculous animals to nonspecific irritants may have a deleterious influence on the tuberculous process. If tubercle bacilli circulate in the blood, as they do from time to time, nonspecific inflammatory processes may reactivate dormant lesions or may even induce the formation of new lesions in the joints, skin and other organs, due to the well known phenomenon of the increased permeability of blood vessels at the site of inflammation. On the other hand, tuberculous animals are at times less sensitive to toxic agents than normal animals. For example, tuberculous animals may tolerate amounts of histamine fatal to normal animals. Hence, anaphylactic phenomena are less pronounced in tuberculous animals. The author stresses the rôle of nonspecific factors such as vascular, nervous, nutritional states etc. on the intensity of the tuberculin skin reaction in tuberculous animals and the inaccuracy of the estimate of the absence of allergic sensitivity on the basis of a negative skin reaction. For this reason she does not accept as decisive the experiments on densensitization as indicating that allergy plays no rôle in immunity, for she maintains that there are no data on the sensitivity of the parenchymal cells in these skin-densitized animals. In line with Bogomolets' observations on reticulo-cytotoxic sera, Drabkina noted that small doses of tuberculin stimulate the growth of allergic cells, whereas larger doses inhibit or kill them.

Judging from the French and German summaries, this Russian book appears to be an interesting and serious investigation of a problem of wide general importance.

ERICH URBACH AND PHILIP M. GOTTLIEB: *Allergy. Second Edition. Pp. xix + 968, with 412 figures and 64 tables, Grunc & Stratton, New York, 1946, fabrikoid, \$12.00.*

By ALBERT H. ROWE

This volume discusses the theoretical, clinical and therapeutic aspects of allergy in a readable, approved and informative manner. Thoughtful study by any physician, including specialists, will increase his knowledge of the subject and his appreciation of the importance of allergic reactivities in patients. The authors and publishers are to be congratulated in presenting this work to our profession.

In the first of the three sections of the book, the fundamental knowledge, based largely on the experimental and clinical researches of the last fifty years, is extensively presented. The relation between allergy, anaphylaxis, atopy and immunity is ably discussed. Various views on allergy and immunity, especially in tuberculosis, are of interest. Theories of the origin of allergy and its effect on the body tissues are considered. Experimental anaphylaxis and allergy are described. The effect of antigens and various recognized antibodies in producing sensitization and the allergic reactions in tissues receive consideration. In this section, also, the methods of testing, the preparations of allergens and the specific and symptomatic measures available for the control of clinical allergy will be found.

In Section 2, most of the recognized and some hypothetical causes of clinical allergy are discussed. Here one finds the most recently recognized allergies, to penicillin, diodrast, gold salts and the important Rh factor. The many causes of contact allergy and the often debatable physical allergies are described. The rôle of bacterial and virus allergy in infectious diseases, producing the clinical manifestations of allergies, receives attention.

The many symptoms arising from allergic reactions in practically all tissues of the body are to be found in Section 3. Thus nasal, sinal, bronchial, gastrointestinal, cutaneous, central nervous system, ocular, aural, cardio-vascular, hematopoetic, joint and genito-urinary manifestations of allergy, as reported in the literature, are disclosed to the reader. Because of the frequency of pollen allergy, the pollens especially necessary to consider in each of nine logical botanical divisions of our country are listed. These lists might have contained a larger number of pollens of secondary importance. References to published surveys in these various areas also would have been helpful, since many allergists believe in treatment with a large number of pollens which the patient inhales, even though skin reactions may be small or absent. The use of very weak dilutions, especially for coseasonal treatment, as advised by Hansel and Rowe, could have been noted in this section.

The discussion of all of these problems is based on many of the important contributions in the literature of the last half century. No attempt to review all of this literature has been made, accounting for the omission of many references which may seem important to various students. Many allergists, more-

over, will disagree with the writers' continued recommendation of propetans for the control of food allergy. Certain procedures which have generally been found inefficacious, such as the oral desensitization to foods, are advised without critical comment. Detailed menus and recipes for the accurate use of elimination diets could have occupied some of the space devoted to directions for the exclusion of single foods, such as egg, milk or wheat. Rarely do we see a patient allergic to only one food.

Future editions might prove of added value if statistics on large numbers of successfully treated patients with various manifestations of allergy were included, from which justified deductions concerning the usual allergenic causes and the best methods of control could be drawn. More case reports with brief specific discussions of the treatment and prolonged follow-up observations would also be valuable.

Books Received

- JOHN FRANCIS: Bovine Tuberculosis. Including a Contrast with Human Tuberculosis. Pp. 220, with 36 illustrations and 21 tables, Staples Press Limited, Cavendish Place, London, W1, 1947, fabrikoid, 25'-net.
- E. GRÄUB: Tuberkulöse Reinfektion beim Rinde und ihr Einfluss auf die Resistenz. Pp. 93, 1947, S. Karger, Basel—New York, paper, Swiss francs 12.
- GERTRUDE E. HODGMAN: A Public Health Survey of Saratoga County, New York, 1945-1946. Pp. 136 + xv, survey made for the Saratoga County Tuberculosis and Public Health Association, Inc., Saratoga Springs, N. Y., paper, \$1.25.
- ARTHUR F. KRAETZER: Procedure in Examination of the Lungs. With Especial Reference to the Diagnosis of Tuberculosis. Third Edition, revised and with a Preface by Jacob Segal. Pp. xviii + 150, with 16 figures and 14 X-ray plates, New York, Oxford University Press, 1947, cloth.
- S. G. LEMAITRE: La Radiophotographie Systématique au Service de la Lutte Anti-Tuberculeuse dans la Région du Nord. Pp. 87, Édité par la Croix-Rouge Française, 12 Square Jussieu, Lille, paper.
- O. M. MISTAL: La Tuberculose dans le Monde. Preface by Prof. G. Bickel. Pp. 496, with 73 illustrations, Librairie Payot, Lausanne, 1947, paper.
- JÓN SIGURDSSON: Studies on the Risk of Infection with Bovine Tuberculosis to the Rural Population. With Special Reference to Pulmonary Tuberculosis. Acta Tuberculosea Scandinavica, Supplementum XV. Pp. 250, Einar Munksgaard, Copenhagen, 1945, paper, Dan. Kr. 15.—.

AMERICAN TRUDEAU SOCIETY¹

Report of the Arizona Trudeau Society

Dr. William H. Oatway, Jr., *Secretary*

The affairs of the Arizona Trudeau Society seem to be in good order at the end of the first year and a half.

The 1946 fall meeting was held in Phoenix in November. Original reports were given on *X-ray Diagnosis of Endobronchial Tuberculosis, Planigraphic Studies and Interpretation* and *Treatment and Pathology of Hemothorax*. Dr. Ray Rumel of Salt Lake City was the guest speaker. He gave a paper on *Resection of Pulmonary Disease*. His expenses were paid by the American Trudeau Society for which the Arizona Society is grateful.

It was decided that the Constitution should be amended to decrease the number of meetings per year from two to one, and preferably to have it in the fall.

A spring letter is being prepared for the members to maintain contact as well as to give recent therapeutic data. The Tucson officers of the Society arranged for the hospital "Depot" distribution of streptomycin during the brief period of such necessity during the past fall.

The officers remain the same for 1947, due to the two-year tenure rule. The officers are: Dr. E. J. Nagoda, President; Dr. Howell Randolph, Vice-President; Dr. Lloyd Swazey, Treasurer; and Dr. William H. Oatway, Jr., Secretary.

Report of the California Trudeau Society

Dr. C. G. Scarborough, *Secretary-Treasurer*

The 1947 annual meeting of the California Trudeau Society will be held in conjunction with the annual meeting of the National Tuberculosis Association in San Francisco in June.

The principal activities of the California Trudeau Society during the year ending March 31, 1947 may be briefly summarized as follows:

Committee Activities

(1) The Committee which was appointed to suggest standards to be used by Health Officers in deciding criteria of communicability in tuberculosis held several meetings and presented its report.

This report was duplicated and sent to each Health Officer in the State.

(2) The Executive Committee of the Society met in San Francisco on October 18, 1946 and discussed future policies with reference to consultative clinics,

¹ All of the section reports published in this section were presented at the 42nd annual meeting of the American Trudeau Society, Medical Section of the National Tuberculosis Association, San Francisco, California, June 14-15, 1947.

postgraduate courses for physicians, examination of groups of patients in local communities under a plan whereby the local physicians of these patients would have the opportunity to be present for a discussion of the films and findings on these patients.

(3) The Committee on Membership was appointed as editing committee for the new Trudeau Society Directory. This preparation of the directory has been completed and it is now ready for printing. The new directory will contain 147 names.

Film Readings

Members of the Society have read an approximate 300,000 X-ray films taken in mass X-ray surveys throughout the State.

Speakers for Medical Societies

An increasing number of County Medical Societies have been supplied with speakers, who have addressed County Medical Society meetings. This is a healthy sign indicating the stimulation of the interest of the local medical societies in our work which has been evidenced during the year.

Fluorograph

One issue of *Fluorograph* was published during the year and mailed to the members.

Correspondence

Replies have been made to various persons who have written the society seeking information upon specific matters.

Report of the Eastern Section of the American Trudeau Society

Dr. N. Stanley Lincoln, *Secretary-Treasurer*

The nineteenth annual meeting of the Eastern Section of the American Trudeau Society was held at the Pennsylvania Hotel in New York City on Friday, November 8, 1946. The Clinical Section on Chronic Pulmonary Diseases of the Tuberculosis Conference of Metropolitan New York jointly sponsored the program and meeting.

After the usual registration, the meeting was called to order at 9:45 a.m. by Dr. Olin Pettingill, who presided. There were present 300 members and guests.

The minutes of the 1944 meeting, held at the Hotel Pennsylvania on January 21, 1944, were read and on motion accepted and ordered filed.

The report of the Secretary was read and, on motion duly made, seconded and unanimously carried, was ordered filed. (Copy added to end of this report.)

The Chairman appointed the following committees:

Auditing Committee

Dr. Arthur M. Stokes of Mt. Morris, N. Y.

Dr. John H. Korns of White Plains, N. Y.

After auditing the accounts, Dr. Stokes moved the acceptance of the Treasurer's report which was unanimously carried and the report ordered filed.

Nominating Committee

Dr. F. Maurice McPhedran of Philadelphia, Pa.

Dr. John Hayes of Saranac Lake, N. Y.

Dr. Hubert Boyle of Cambridge, Mass.

This committee reported as follows:

President	Dr. David A. Cooper of Philadelphia, Pa.
Vice-President	Dr. Herbert R. Edwards of New York City
Secretary-Treasurer	Dr. N. Stanley Lincoln, Ithaca, N. Y.

There being no nominations from the floor, on motion duly made, the Secretary was ordered to cast a unanimous ballot for the slate as proposed.

The following new members were proposed and, on motion made by Dr. McPhedran, duly seconded and carried, the Secretary was ordered to cast a unanimous ballot for their election.

Active Members

Dr. Nathan A. Goldstein, Flushing, N. Y.

Dr. Horace C. Reider, Bryn Mawr, Pa.

Dr. Marguerite D. Shepard, Hartford, Conn.

Dr. Alfred Ring, Jamaica, N. Y.

Dr. William P. McHugh, Cambridge, Mass.

Dr. Otto Brantigan, Baltimore, Md.

Dr. Arthur Robins, New York City

Dr. Raymond C. Ryan, Jamaica, N. Y.

Dr. Harry Epstein, Jamaica, N. Y.

Dr. John B. O'Connor, Trudeau, N. Y.

Associate Members

Dr. John Cannon, Scarsdale, N. Y. Dr. Gordon Meade, Rochester, N. Y.

The scientific and luncheon meetings were held following the business session as indicated in the program.

Doctor Childress, Chairman of the Clinical Section of the Tuberculosis Sanatorium Conference, presided at the afternoon scientific session.

On motion duly made and seconded the meeting was adjourned.

Secretary's Report

In 1945, the membership was polled and a very real interest in a Section Meeting was expressed. But due to food rationing, restrictions on travel and shortage

of hotel space, it became apparent to the officers that it was not feasible to attempt a Section Meeting.

At the present time, the membership data are as follows:

1. Active members.....	206, including 26 still in military service
2. Associate members.....	53, including 13 still in military service
3. Emeritus.....	2
<hr/>	
4. Total.....	261

Since the previous meeting in January, 1944, 11 members have passed from us to their Great Reward; and 20 more have resigned, transferred to other sections or have been lost. Because there has been no opportunity for the election of new members, our present roster is definitely below its normal strength. Dr. Guild, former Executive Secretary of the American Trudeau Society, advised that the total membership of that body in the states covered by our Section is 850.

It should be recalled that associate members are those who are not members of the parent organization—The American Trudeau Society. Due to the exigencies of war, the Secretary has not taken any action with respect to the termination of associate membership of those who did not join the American Trudeau Society within the prescribed period of three years. It seems that in the coming year, when things have reverted to normal, the by-laws and regulations might be tactfully applied.

With respect to dues, the membership has been notably loyal. There are only 11 whose dues are in arrears three or more years, 9 whose dues are in arrears two years and 69 who have not paid for 1945.

The Section has no record of the military service of its members, except the lone fact that some were in service. If it is desirable that the Section archives contain data of this nature, then the individual members should forward such data.

Suggestions as to how your Secretary can serve you better are always welcome.

Report of the Florida Trudeau Society

Dr. R. D. Thompson, *President*

At the annual meeting of the State Tuberculosis and Health Association held in Miami on May 1-2, 1947, there was organized a Florida section of the American Trudeau Society with twenty-one physicians signed up. In addition there are many others who belong to the American Trudeau Society but were not at the meeting and who will become members of the Florida Trudeau Society.

Of course, the Florida Society will act as the Medical Section of our State Tuberculosis and Health Association and will always meet at a time when the State Association has its meeting. The officers will act as a Program Committee

for the Medical Section lending every assistance possible to the State Association. The officers elected were the following:

President	R. D. Thompson, M.D., Orlando, Florida
Vice-President	Isaac C. Clippes, M.D., Miami, Florida
Secretary-Treasurer	C. M. Sharp, M.D., Jacksonville, Florida

Report of the Illinois Trudeau Society

Dr. L. L. Collins, *Secretary-Treasurer*

We are planning a luncheon and X-ray presentation program in connection with the Illinois Tuberculosis Association's annual meeting to be held in Peoria the 28th and 29th of April. We also have a meeting planned in the early part of October with the Sangamon Medical Society at Springfield, Illinois.

A summary of a meeting held on December 10, 1946, follows: The regular fall meeting of the Illinois Trudeau Society was held in conjunction with the Medical Society meeting at Lake County Sanatorium, Waukegan, Illinois, on December 10, 1946, and was called to order at 2:15 p.m. by the President, Dr. Loewen. There were about 27 present for the afternoon meeting.

The first paper was by Dr. L. E. Joslyn, from the Abbott Laboratories, and his subject was *Sulfones and Streptomycin in Acid-fast Infections*. Dr. Joslyn's paper was discussed by Dr. Sweany and Dr. Petter.

The second paper was by Dr. M. Joannides, Chicago, Illinois. His subject was *Experiences with Differential Pressure Chamber*. Dr. Joannides showed slides and moving pictures demonstrating the action of the iron lung on tuberculosis. Dr. Joannides then gave a report on some person treated by this method. He expressed the opinion that this method of treatment has some possibilities. His paper was discussed by Dr. Bullen and also by Dr. Loewen.

The third paper was by Dr. E. A. Piszczek, Chicago, Illinois. His subject was *State Subsidy for Care of Tuberculous Patients*. This paper brought out a rather large discussion by Dr. Tucker, Dr. Bryan, Dr. Newitt and Mr. Shahan.

The fourth paper was by Dr. V. A. Lennarson, Waukegan, Illinois. He presented a case of *Tuberculosis of the Inner Ear*. The case was a boy aged 10 years who had a paralysis of the left side of his face and a tuberculosis of the temporal bone. A recess of fifteen minutes followed the discussion of the last paper.

A business meeting was called to order by the President, Dr. Loewen, at 5:30 p.m. . . . Dr. Bosworth, chairman of the nominating committee, presented the following slate for the consideration of the members of the Trudeau Society: President, Dr. Petter; President-Elect, Dr. Bulley; Vice-President, Dr. Webb; Secretary-Treasurer, Dr. L. L. Collins. Two members for the executive committee, Dr. Loewen and Dr. Turner. Dr. Bosworth moved that the report of the

nominating committee be accepted and that a unanimous ballot be cast for the persons nominated. Dr. Bryan seconded the motion. Motion carried.

Dr. Bryan then presented a request by Dr. Herbolzheimer of the State Department of Health requesting that the Illinois Trudeau Society make recommendations for the tuberculosis control program in the State of Illinois. A committee was appointed and this committee met at Rockford at 1:00 p.m. on December 8, 1946. Those present were: Chairman, W. J. Bryan, M.D.; Robinson Bosworth, M.D.; Kenneth Bulley, M.D.; Charles Petter, M.D.; and Arthur Webb, M.D. Mr. W. P. Shahan, Executive Secretary of the Illinois Tuberculosis Association, was present by invitation and acted in an advisory capacity.

Consideration was given as to the advisability of developing tuberculosis divisions in general hospitals in lieu of sanatoria. The committee, however, felt that this was not wise; and Dr. Bosworth moved that, because the need for tuberculosis beds is great in several areas of the State of Illinois, and because tuberculosis departments or divisions of general hospitals may not be expected to solve the problem satisfactorily, and because due regard should be given to the fact that the care of tuberculous patients in the State of Illinois be financed by specially authorized sanatorium taxes, and because such monies set aside for tuberculosis should be used for the control and eradication of tuberculosis, and because the establishment of wings or divisions in general hospitals might be conducive to the use of such funds for other purposes, and because the recognized difference in the per capita cost of general hospitals and sanatoria might result in increased costs in the care of such tuberculous patients, and because such an arrangement might bring about the neglect of proper epidemiological programs, therefore, be it resolved that this committee is not in favor of the construction or setting aside of tuberculosis divisions in general hospitals for the care of tuberculous patients at this time. The motion was seconded and carried unanimously.

The committee, however, did not wish to discourage the care of tuberculous patients in general hospitals and recommends that any teaching hospital set aside not over 10 per cent of its beds for the diagnosis, study and outline of treatment of tuberculosis patients for teaching purposes among its doctors, internes, residents, students, and nurses, but that such patients should not receive permanent sanatorium care in such general hospitals. The committee, therefore, recommends that all general hospitals be encouraged to establish communicable disease wards and that tuberculosis be considered in the same light as other communicable diseases. The committee further recommends and urges that all general hospitals establish tuberculosis case-finding procedures among its staff and patients and that all patients in the out-patient department, as well as those admitted to the hospital proper, receive an X-ray film of the chest as part of their general physical examination. It is also recommended that the staff and employees have X-rays of the chest at regular intervals.

AMERICAN TRUDEAU SOCIETY

Following dinner, Dr. C. H. Harrison, Waukegan, Illinois, gave a very interesting and informative paper on *Ocular Tuberculosis*. He presented a very interesting case. Many of those present viewed the eye ground with an ophthalmoscope. A Clinical-Pathological Conference on *Diseases of the Chest* was conducted by Dr. J. C. McCarter, Evanston, Illinois. Several very interesting chest cases were presented and discussed by those present.

Report of the Indiana Trudeau Society

M. A. Auerbach, *Executive Secretary*

The annual meeting of the Indiana Trudeau Society was held May 7, 1947 at the Lincoln Hotel, Indianapolis, and, following the usual short business session, the following program was given:

Resection for Pulmonary Tuberculosis—Francis X. Byron, M.D., Section of Thoracic Surgery, University Hospital, Ann Arbor, Michigan.
Laboratory Methods of the State Board of Health with Particular Reference to Tuberculosis—Samuel Damon, Ph.D., Director, Bureau of Laboratories, Indiana State Board of Health.

12:00 noon—Luncheon.

Chemotherapy in Tuberculosis with Special Reference to Streptomycin—Karl H. Pfuetze, M.D., Superintendent and Medical Director, Mineral Springs Sanatorium, Cannon Falls, Minnesota.

In the afternoon a joint session was held with the Indiana Tuberculosis Association as follows:

Some Aspects of Sensitivity to Histoplasmin and Tuberculin—Michael L. Furcolow, M.D., Kansas City, Missouri.

Management of Tuberculosis in Heavy Industry—E. H. Carleton, M.D., Inland Steel Corporation, East Chicago, Illinois.

Case-work in the Psychosomatic Approach to the Tuberculous Patient—Jeanette Hertzman, Assistant Chief, Social Service Section, Veterans Administration, St. Louis, Missouri.

The Chest Survey in a General Hospital—Harold C. Ochsner, M.D., Methodist Hospital, Indianapolis, Indiana.

The elected officers are:

President	—Hubert B. Pirkle, M.D., Rockville
President-Elect	—O. T. Kidder, M.D., Fort Wayne
Vice-President	—Thomas R. Owens, M.D., Muncie
Secretary-Treasurer	—C. J. McIntyre, M.D., Indianapolis
Executive Secretary	—M. A. Auerbach, Indianapolis

Report of the Trudeau Society of Los Angeles

Dr. Arthur E. T. Rogers, *Secretary-Treasurer*

The roster of active members of the Los Angeles Trudeau Society has passed the number of one hundred during the year of 1947, with the following serving as officers for the current year:

President	Edward S. Kupka, M.D.
Vice-President	Joseph L. Robinson, M.D.
Secretary-Treasurer	Arthur E. T. Rogers, M.D.

Regular business and scientific meetings have been held every month, including symposia prepared by the staffs of the Olive View Sanatorium, the San Fernando Veterans Administration Hospital and the Los Angeles Sanatorium. A joint meeting was also held with the Section on Radiology of the Los Angeles County Medical Association.

Attendance at the various meetings varied from 50 to 70 per cent of the membership, and papers covering many aspects of chest diseases were presented, with considerable emphasis on tracheobronchial tuberculosis, streptomycin therapy in tuberculosis and its complications, and pulmonary resection in the treatment of tuberculosis and malignancy.

The Society meets on the fourth Tuesday of every month from October to May, and physicians visiting the West Coast are always welcome guests.

Report of the Massachusetts Trudeau Society

Dr. William R. Martin, *Secretary-Treasurer*

The Massachusetts Trudeau Society held three regular meetings during the year 1946, in January, May and October. These meetings, since the onset of the war, have been held at the Harvard Club, Boston. Beginning with the next meeting in May, 1947, we are planning to resume our custom of meeting at the various sanatoria throughout the State.

At the fall meeting in October, it was voted to increase the membership from 100 to 125 in order to admit new members. The present membership is 105.

The present officers are:

Dr. Richard Sweet	—President
Dr. Donald King	—Vice-President
Dr. William R. Martin	—Secretary-Treasurer

Officers are elected for the year at the annual meeting which is held in May.

Report of the Michigan Trudeau Society

Dr. L. C. Manni, *Secretary-Treasurer*

The annual meeting of the Michigan Trudeau Society was held on November 7, 1946 in Detroit, Michigan.

At this meeting it was planned to have two meetings in 1947—the Spring meeting to be held with the Michigan Tuberculosis Association. The following officers Forty-one new members were elected to membership. The following officers were elected to serve until the Spring meeting of 1947:

Charles R. Smith, M.D., President
W. L. Brosius, M.D., Vice-President
L. C. Manni, M.D., Secretary-Treasurer

Report of the Minnesota Trudeau Medical Society

Dr. Clarence Siegel, *Secretary-Treasurer*

The following is a report of the proceedings of the Minnesota Trudeau Medical Society, beginning June 1, 1946.

The annual summer meeting of the Minnesota Trudeau Medical Society was held at Nopeming Sanatorium, Nopeming, Minnesota, on July 8, 1946.

Dr. Fenger gave a report of the Sanatorium Consultation Committee which met at Brainard, Minnesota, on April 28, 1946. Cases were discussed from the following Sanatoria with recommendations for treatment: Otter Tail County, Lake Park, Sand Beach, Lake Julia, Fair Oakes Lodge, Deerwood Sanatorium.

This committee met again at Pembine, Wisconsin, with the Michigan and Wisconsin groups. Various cases of thoracoplasty, phrenic, and pneumothorax operations were presented and discussed by each state.

The following scientific program was presented:

Activities of the Nopeming Sanatorium Outpatient Department—Dr. Robert Davies, Nopeming, Minnesota.

Pneumoperitoneum—Dr. Sam Sandell.

Pneumothorax—Drs. Clive R. Johnson and Gustav A. Hedberg.

The annual meeting of the Minnesota Trudeau Medical Society was held at the Lowry Hotel, St. Paul, Minnesota, on November 8, 1946. Forty-five members and guests were present.

Dr. Fenger gave a report of the Sanatorium Advisory Committee which had met at Walker, Minnesota, on October 11 and 12, 1946. Forty-eight Indian patients were discussed and suggestions made regarding treatment.

The Nominating Committee, consisting of Doctors Mattill, Sandell and Huban, made the following report:

Dr. Corwin Hinshaw—President
Dr. E. P. K. Fenger—Vice-President
Dr. Clarence Siegel—Secretary-Treasurer

The report of the Nominating Committee was unanimously accepted. The following scientific programs were presented:

Treatment of Hemorrhage—Dr. R. V. Ebert.

Differential Diagnosis of Pulmonary Masses—Dr. Dan Fink.

A moving picture *Technique of Mass X-ray Survey*—State Department of Health.

The annual winter meeting of the Minnesota Trudeau Medical Society was held at the Nicolet Hotel, Minneapolis, Minnesota, on January 31, 1947. Fifty members and guests were present.

Dr. Fenger also reviewed the functions of the Pembine meeting. This meeting will be held in September, 1947. A motion was made and seconded that the additional seven men be chosen by the president to attend this meeting.

Dr. Sandell suggested that, in view of the money the society had, a guest speaker be asked to be on the program in the future, and that the society pay his expenses.

A motion was made by Dr. Hedberg and seconded by Dr. Mariette that the Executive Committee be authorized to choose a guest speaker to talk on BCG or otherwise, the society paying his expenses.

The following scientific program was presented:

Early Diagnosis of Cancer of the Lung—Dr. Leo Rigler.

Some Difficulties in Diagnosing Cancer of the Lung—Dr. Frances King.

The annual spring meeting of the Minnesota Trudeau Medical Society will be held at the Mayo Foundation House on Tuesday, May 20, 1947. A luncheon at the Mayo Foundation House will be held at 12:00 noon.

The following scientific program will be presented:

Technique and Discovery of Malignant Cells in Sputum—Dr. J. R. McDonald, Rochester, Minnesota.

New Data on Correlation between Mitral Stenosis and Pulmonary Tuberculosis—Dr. D. T. Carr, Rochester, Minnesota.

Tracheobronchial Tuberculosis Treated with Streptomycin—Dr. A. M. Olson, Rochester, Minnesota.

Upper Lobe Carcinoma Which Might Be Confused with Tuberculosis—Dr. O. T. Clagett and associates, Rochester, Minnesota.

Report of the Mississippi Valley Trudeau Society

Dr. John D. Steele, *Secretary*

The 1946 meeting of the Mississippi Valley Trudeau Society was held at the Hotel Sherman, Chicago, Illinois, on September 26 and 27. The medical program was of excellent quality and was well received. Free discussion took place on practically all papers, being especially free following the papers presented by Doctor Holm and Doctor Custer.

The following program was presented:

Thursday, September 26

9:00 a.m.

Epidural Anesthesia in Thoracic Surgery—Y. F. Fujikawa, M.D., Arnaldo Neves, M.D., C. A. Brasher, M.D., Mt. Vernon, Missouri; and W. W. Buckingham, M.D., Kansas City, Missouri.

A Method of Performing Bilateral Bronchographic Studies—H. W. Schmidt, M.D., Rochester, Minnesota.

The Diagnosis of Right Heart Enlargement by Angiocardiography (A Preliminary Report)—Nathan Grossman, M.D., Milwaukee, Wisconsin.

BCG Vaccination in Denmark—Johannes Holm, M.D., Copenhagen, Denmark.

2:00 p.m.

Current Medical Research in Tuberculosis—Henry Stuart Willis, M.D., Detroit, Michigan.

The Need for Coöperation in Rehabilitation of the Tuberculous—C. K. Himmelsbach, M.D., Sr. Surgeon, U.S.P.H.S., Chicago.

The Physician's Role in Rehabilitation of the Tuberculous—Norvin C. Kiefer, M.D., Surgeon, U.S.P.H.S., Washington, D. C.

Discussion.

Our Voluntary Health Agencies—William P. Shepard, M.D., President, National Tuberculosis Association, San Francisco, California.

Tuberculosis Control among Hospital Personnel—H. McLeod Riggins, M.D., President, American Trudeau Society, New York, New York.

Discussion.

8:30 p.m.

X-ray Conference.

Friday, September 27

9:00 a.m.

Evaluation of 1945 Thoracic Surgery in a County Tuberculosis Hospital—Karl P. Klasen, M.D., George M. Curtis, M.D., and W. L. Potts, M.D., Columbus, Ohio.

Pregnancy Occurring in a Group of Tuberculous Women—Gertrude F. Mitchell, M.D., Detroit, Michigan.

Analysis of Tuberculin Testing in a Large Sanatorium—M. R. Lichtenstein, M.D., Chicago, Illinois.

Tuberculosis Control through Coöperation—Edward W. Custer, M.D., South Bend, Indiana.

The business session was held on September 27 with Dr. E. S. Mariette presiding. The president called for the report of the nominating committee. This committee, consisting of Drs. F. L. Jennings, A. A. Pleyte and W. J. Bryan, presented the following nominations:

President-Elect—Dr. Herbert L. Mantz

Vice-President—Dr. Paul D. Crimm

Secretary—Dr. John D. Steele

These candidates were elected by unanimous ballot.

Report of the Missouri Trudeau Society

Dr. D. L. Coffman, *Secretary-Treasurer*

The annual meeting of the Missouri Chapter, American Trudeau Society, was held Saturday, October 19, 1946, at 7:30 p.m., Hotel Missouri, Jefferson City, Missouri; E. E. Glenn, M.D., President, presiding. The following were present: R. M. James, M.D.; W. L. Gist, M.D.; Geo. D. Kettelkamp, M.D.; W. G. Gunn, M.D.; Chas. A. Brasher, M.D.; Newell R. Ziegler, M.D.; T. E. Huber, M.D.; John Kalish, M.D.; Bernard Friedman, M.D.; H. S. Miller, M.D.; Ira Lockwood, M.D.; H. L. Mantz, M.D.; John A. Saston, M.D.

The minutes of the previous meeting were read and approved.

The Nominating Committee reported the following slate:

President-Elect —Paul Murphy, M.D., St. Louis
Secretary-Treasurer—D. L. Coffman, M.D., Kansas City

Executive Committee

E. E. Glenn, M.D., Springfield
Geo. D. Kettelkamp, M.D., St. Louis

Moved by Dr. Mantz that the report be accepted and the secretary instructed to cast the ballot. Seconded by Dr. Miller. Carried.

Report of Membership Committee by Dr. Mantz on qualifications for membership.

Old business—None.

New business—The executive secretary was instructed to enlarge the membership list and be sure to include all St. Louis Trudeau members.

Dr. Mantz, Program Committee, spoke regarding next meeting. There was general discussion of time, place and contacts.

Dr. Kettelkamp reported on the Tri-State Conference, Coronado Hotel, St. Louis, February 9 and 10, 1946.

Dr. Mantz discussed the 1947 Tri-State meeting to be held February 22-23, Hotel Edgewater Beach, Chicago, Illinois. The sanatoria to report are: Mount Vernon (Missouri State Sanatorium), Chicago Municipal Tuberculosis Sanitarium, and Sunnyside of Indianapolis. There will be 60 cases from each institution—consecutive cases starting July 1, 1944.

Dr. R. M. James, Division of Health, spoke briefly.

The meeting was turned over to Dr. Mantz, Program Chairman, for the scientific session.

The Tri-State Trudeau Society (Missouri, Indiana and Illinois) met at the Edgewater Beach Hotel, Chicago, February 22 and 23, 1947.

The Missouri State Sanatorium, Chicago Municipal Sanitarium and the Marian County of Indianapolis Sanatorium each presented 60 consecutive admissions from January 1, 1945. Response at this meeting was much better than last because it was felt those in attendance were becoming more familiar with one another.

The Missouri Trudeau Society met again March 30, 1947, at the Hotel President, Kansas City, Missouri, just prior to the meeting of the Missouri State Medical Society. An excellent program was presented and ended with an X-ray conference in which a number of interesting and unusual films were presented.

Results of the election of officers:

President-Elect	—Jesse E. Douglas, M.D.
Executive Committee Member	—H. L. Mantz, M.D.
Secretary-Treasurer	—D. L. Coffman, M.D.

Report of the South Carolina Trudeau Society

Dr. Samuel E. Miller, *Secretary and Treasurer*

The South Carolina Trudeau Society met at the Wade Hampton Office Building, Columbia, South Carolina, November 1, 1946.

Doctor W. Atmar Smith, Vice-President, presided.

Doctor John M. Preston acted as Secretary and Treasurer, in the place of Doctor John F. Busch.

Fourteen physicians were present.

The following officers were elected:

President	—Dr. John M. Preston, Columbia
Vice-President	—Dr. David B. Gregg, Charleston
Secretary and Treasurer	—Dr. Samuel E. Miller, State Park

Treasurer reported income of sixteen dollars without any disbursements for past year.

Dues of one dollar each were collected from each member present for current year.

Resolution was adopted for the appointment, by the President, of a committee to consult with the State Division of Tuberculosis Control on the matter of *Minimum Standards for Physicians, Technicians, Laboratories and Others*, who are to aid that department in tuberculosis work.

These appointments will be made by the President at a later date.

The scientific program consisted of an address, with lantern slides and X-ray films, by Dr. David Waterman of Knoxville, Tennessee. His subject was *An Evaluation of Extrapleural Thoracoplasty*. He discussed the history of thoracoplasty, improvement in technique, the lower mortality, selection of cases, operative technique, complications and end-results.

Report of the Southern Trudeau Society

Dr. J. B. Naive, *Secretary-Treasurer*

The Southern Trudeau Society met in the Assembly Room of the Mayflower Hotel, Jacksonville, Florida, on October 3, 1946. The occasion was a luncheon and reorganizational affair, there being no formal program. The meeting was under the direction of the President, Dr. Duane Carr.

Officers elected were:

President —Dr. Kellie Joseph, Birmingham, Alabama
Vice-President—Dr. M. D. Bonner, Jamestown, North Carolina
Secretary —Dr. J. B. Naive, Knoxville, Tennessee

In a general discussion regarding future programs, it was the consensus that such programs should, as far as possible, take the pre-war form, that X-ray clinics should be strongly stressed and that an effort should be made to develop the strongest possible one-day scientific program. The officers were instructed to act as a program committee and were further instructed to participate with the program committee of the Southern Tuberculosis Association in the development of a program for the 1947 meeting. It was unanimously voted to request the "time and place committee" of the Southern Tuberculosis Association to hold that meeting in Birmingham, Alabama. A total of 39 were present.

There will be another meeting of the Southern Trudeau Association to be held in connection with the next meeting of the Southern Tuberculosis Conference. This meeting will be held at the Rice Hotel, Houston, Texas, October 2, 3 and 4, 1947.

Report of the Texas Trudeau Society

Dr. T. R. Jones, *Secretary*

The Texas Trudeau Society was organized primarily as a sponsoring group for the Scientific Section of annual meetings of the Texas Tuberculosis Association. The Society assumed full responsibility for the Scientific Section of our 1946 annual meeting, and is doing the same thing this year—in fact, plans for the 1947 program are practically complete.

There follows the minutes of the 1946 meeting of the Texas Trudeau Society.

The Texas Chapter of the American Trudeau Society met in Houston at luncheon in the Rice Hotel on Monday, September 16, 1946, during the annual meeting of the Texas Tuberculosis Association. The meeting was called to order by the President, Dr. H. Frank Carman. A total of 42 physicians were present.

In opening the meeting Dr. Carman expressed the thanks of the Chapter for the excellent program prepared for the medical section of the annual meeting

under the direction of Dr. J. Edward Johnson, Chairman of the Program Committee. Those serving with Dr. Johnson were Dr. E. G. Faber, Tyler; Dr. James E. Dailey, Houston; Dr. Howard E. Smith, Austin; Dr. Robert J. Nanks, Waco.

Minutes of the previous meeting of the Chapter, held in Austin on September 18, 1944, were approved as read. Attention was called to the fact that no meeting of the Society had been held since the organization meeting on that date, due to conditions of war which precluded large gatherings because of the difficulty of travel.

Report of the Nominating Committee was presented by the Chairman, Dr. J. Edward Johnson. The following slate was nominated to serve for the fiscal period 1946-1947:

President	—Dr. E. G. Faber, Tyler
President-Elect	—Dr. Elliott Mendenhall, Dallas
Vice-President	—Dr. James E. Dailey, Houston
Secretary	—Dr. Thomas R. Jones, Houston

There being no nominations from the floor, on motion by Dr. J. B. McKnight the report of the Nominating Committee was adopted and these officers duly elected.

Attending the luncheon as a guest was Dr. Ward L. Moald, Surgeon, U.S.P.H.S., Assistant Regional Representative, Federal Security Agency, Office of Vocational Rehabilitation, Kansas City, Missouri, who congratulated the Society on the fine scientific program prepared for the medical section. Dr. Moald spoke briefly on vocational rehabilitation and its relation to the tuberculosis patient, stressing the important rôle which the physician plays in the program. He expressed appreciation for the coöperation which is being given Mr. J. J. Brown, Director of Vocational Rehabilitation in Texas, by members of the medical profession.

Dr. Carman commended the program of rehabilitation being carried on in Texas, saying that patients can be returned to work without any difficulty through the rehabilitation service. He extended the thanks of members of the Society to Dr. Moald for his attendance at the meeting.

There being no further business, the meeting was declared adjourned. These minutes were presented by Dr. Mendenhall, former Secretary of the Society.

Report of the Wisconsin Trudeau Society

Dr. Helen A. Dickie, *Secretary-Treasurer*

The Wisconsin Trudeau Society met at Lake View Sanatorium on April 26, 1947.

The entire meeting was devoted to the use of streptomycin in tuberculous disease. The first part of the meeting consisted of presentations of the cases

which had been treated from four sanatoria. Dr. Nicholas D'Esopo of Sunmount, New York, reported 25 cases which had completed 120 days of streptomycin therapy. The usual dosage was 1.8 grams per day. All of the patients had tubercle bacilli in the pulmonary secretions which were sensitive to streptomycin. At the end of four months of treatment 50 per cent of these patients' sputum contained tubercle bacilli which were highly resistant to streptomycin. Eleven of the 25 patients remained sputum-positive by smear and in all of them the organisms were resistant at the end of the period of treatment. Dr. D'Esopo concluded that exudative disease responds well initially and that cavities seldom close with streptomycin therapy. There appears to be a definite correlation between sensitivity of the tubercle bacillus to streptomycin and the therapeutic response.

Presentations of somewhat smaller groups of streptomycin-treated cases were given by Dr. G. D. Guilbert from Wood, Wisconsin; Dr. J. C. Dundee from the Veterans Hospital at Waukesha, Wisconsin; and Dr. D. Gutheil of Muirdale Sanatorium. Their results were essentially the same as noted previously, that is, many cases showed early response, but that cavity closure and complete control were seldom realized except in the early predominantly exudative lesion.

Dr. Guy P. Youmans of Northwestern University presented a paper on *The Effect of Streptomycin Therapy on Tubercle Bacilli in vitro and in vivo*. He found that all the tubercle bacilli studied were sensitive to streptomycin initially, but that the degree of sensitivity varied with strains. Twenty-nine of 131 cultures required more than one microgram of streptomycin per milliliter to inhibit growth initially. If the tubercle bacilli were exposed and reexposed through culture transfers to streptomycin a marked resistance to the drug occurred in fifty-two to 120 days. Mice infected with streptomycin-resistant strains of tubercle bacilli were not protected by streptomycin. The significance and probable method of development of resistance was discussed.

Dr. Karl Pfuetze of Cannon Falls, Minnesota, stressed the importance of making use of the temporary control of the disease to proceed with the usual and accepted forms of collapse therapy. For a certain number of patients, streptomycin can be of great value in controlling the toxemia and recent spreads so that major collapse methods can be done to combat the older foci, especially cavitation, which respond poorly to the drug.

A short business meeting was held. The major discussion was concerned with joining the Wisconsin Anti-Tuberculosis Association as a group. A constitution was submitted by the committee composed of Drs. Schmidt, Daniels and Feld. This was accepted by the members and will be presented to the Board of Directors of the Wisconsin Anti-Tuberculosis Association for their approval. Dr. Feld was elected as the fifth member of the executive council.

AMERICAN TRUDEAU SOCIETY

At the meeting of the Council held in Houston, Texas on September 30, 1947, the following appointments to committees for 1947-1948 were confirmed.

I. Administrative¹

Budget Committee

Howard W. Bosworth, M.D.
H. Corwin Hinshaw, M.D.
David A. Cooper, M.D.
Henry Stuart Willis, M.D.
H. McLeod Riggins, M.D.
Theodore L. Badger, M.D.

Nominating Committee

Sidney J. Shipman, M.D., *Chairman*
John H. Skavlem, M.D.
Rollin D. Thompson, M.D.

Membership Committee

Chesley Bush, M.D., *Chairman*
Grover C. Bellinger, M.D.
Russell S. Henry, M.D.

Constitution and By-Laws Revision

Carl R. Howson, M.D., *Chairman*
Herbert R. Edwards, M.D.
Ralph Horton, M.D.
H. McLeod Riggins, M.D.
John D. Steele, M.D.

II. Professional Education

American Review of Tuberculosis

Official Journal—Editorial Board

Emil Bogen, M.D.	Lewis J. Moorman, M.D.
Halbert L. Dunn, M.D.	D. W. Richards, Jr., M.D.
Ross Golden, M.D.	William P. Shepard, M.D.
A. J. Lanza, M.D.	Sidney J. Shipman, M.D.
Herbert C. Maier, M.D.	John D. Steele, M.D.

C. Eugene Woodruff, M.D.

Annual Meeting Program (Medical Session)

Herbert C. Maier, M.D., Chairman

W. Reece Berryhill, M.D.	Arthur W. Newitt, M.D.
Cedric Northrop, M.D.	Arthur M. Stokes, M.D.
Max Pinner, M.D. (<i>ex officio</i>)	

Diagnostic Standards Revision (1) (2)

Ralph Horton, M.D., Chairman

Ezra Bridge, M.D.	Oscar A. Sander, M.D.
W. Edward Chamberlain, M.D.	John D. Steele, M.D.
Herman E. Hilleboe, M.D.	Ismael Cosio Villegas, M.D.
Edgar Medlar, M.D.	George J. Wherrett, M.D.
Hector Orrego Puelma, M.D.	Roy A. Wolford, M.D.

¹ The members of the Executive Committee, the Council and the Advisory Board were listed on page 609 of the December, 1947 issue of the *Review*.

- (1) *Subcommittee on Evaluation of Laboratory Procedures*
 C. Eugene Woodruff, M.D., *Chairman*
 Emil Bogen, M.D.
 Edwin A. Doane, M.D.
 M. L. Furcolow, M.D.
 Max Lurie, M.D.
 Edgar Medlar, M.D.
 Mr. William Steenken (NTA)
- (2) *Subcommittee on Tuberculin Testing*
 Joseph D. Aronson, M.D., *Chairman*
 Florence B. Seibert, Sc.D.
 Carroll E. Palmer, M.D.
 Sol Roy Rosenthal, M.D.

Medical Education—National Committee (1) (2)

- Kirby S. Howlett, Jr., M.D., *Chairman*
 Theodore L. Badger, M.D.
 John B. Barnwell, M.D.
 Robert G. Bloch, M.D.
 Paul T. Chapman, M.D.
 Kendall Emerson, M.D.
 Herman E. Hilleboe, M.D.
 Edward N. Packard, M.D.
 Howard M. Payne, M.D.
- Max Pinner, M.D.
 John D. Steele, M.D. (*Secretary*)
 Harold G. Trimble, M.D.
 James J. Waring, M.D.
 George J. Wherrett, M.D.
 Henry Stuart Willis, M.D.
 Julius L. Wilson, M.D.
 Mr. C. W. Kammeier (NCTS)

- (1) *Subcommittee on Faculty and Curriculum*
 John D. Steele, M.D., *Chairman*
 Theodore L. Badger, M.D.
 Esmond R. Long, M.D.
- (2) *Subcommittee on Courses for the General Practitioner*
 Harold G. Trimble, M.D., *Chairman*
 Herman E. Hilleboe, M.D.
 J. A. Myers, M.D.
 Edwin J. Simons, M.D.

Committee on Medical Education

Region I

- Theodore L. Badger, M.D., *Chairman*
 Donald S. King, M.D., *Co-Chairman*
 Hugh B. Campbell, M.D.
 John C. Ham, M.D.
 Kirby S. Howlett, Jr., M.D.
 Paul S. Phelps, M.D.
 Alton S. Pope, M.D.
 John W. Strieder, M.D.
 Miss Mabel Baird (NCTS)

Region II

- Edward N. Packard, M.D., *Chairman*
 Herbert R. Edwards, M.D., *Co-Chairman*
 J. Burns Amberson, M.D.
 David A. Cooper, M.D.
 John Gibbon, M.D.
 C. Howard Marey, M.D.
 Russell E. Teague, M.D.
 Mr. G. Taggart Evans (NCTS)

Region III

- Henry Stuart Willis, M.D., *Chairman*
 Howard Bradshaw, M.D., *Co-Chairman*
 Thomas B. Aycock, M.D.
 W. Reece Berryhill, M.D.
 Rufus F. Payne, M.D.
 David T. Smith, M.D.
 W. Atmar Smith, M.D.
 Rollin D. Thompson, M.D.
 David H. Waterman, M.D.
 Mr. Frank W. Webster (NCTS)

Region IV

- Julius L. Wilson, M.D., *Chairman*
 Sidney Jacobs, M.D., *Co-Chairman*
 Henry Boswell, M.D.
 Maurice Campagna, M.D.
 H. Frank Carman, M.D.
 Lewis J. Moorman, M.D.
 Robert R. Shaw, M.D.
 Miss Pansy Nichols (NCTS)

Region V

Paul T. Chapman, M.D., *Chairman*
 John H. Skavlem, M.D., *Co-Chairman*
 Robert G. Bloch, M.D.
 Harold M. Coon, M.D.
 Bruce H. Douglas, M.D.
 H. Corwin Hinshaw, M.D.
 Frank L. Jennings, M.D.
 Herbert L. Mantz, M.D.
 John D. Steele, M.D.
 Henry C. Sweany, M.D.
 Mr. Theodore J. Werle (NCTS)

Stuart Sanger, M.D.
 Miss Helen L. Burke (NCTS)

Region VII

Harold G. Trimble, M.D., *Chairman*
 Sidney J. Shipman, M.D., *Co-Chairman*
 Grover C. Bellinger, M.D.
 Emil Bogen, M.D.
 Carl R. Howson, M.D.
 John C. Jones, M.D.
 Cedric Northrop, M.D.
 Mr. W. Ford Higby (NCTS)

Region VI

James J. Waring, M.D., *Chairman*
 H. Dumont Clark, M.D., *Co-Chairman*
 John F. Allen, M.D.
 F. R. Harper, M.D.
 Allan Hurst, M.D.
 Carl Mulky, M.D.

Region VIII

George J. Wherrett, M.D., *Chairman*
 Hugh E. Burke, M.D., *Co-Chairman*
 James D. Adamson, M.D.
 Robert G. Ferguson, M.D.
 William H. Hatfield, M.D.
 R. M. Janes, M.D.

Medical Information Committee

William G. Childress, M.D., *Chairman*
 Ezra Bridge, M.D.
 Dean B. Cole, M.D.
 Edward W. Custer, M.D.
 Paul Dufault, M.D.
 Cedric Northrop, M.D.
 David E. Quinn, M.D.
 Raymond H. Runde, M.D.
 C. M. Sharp, M.D.
 Russell E. Teague, M.D.
 Peter A. Theodos, M.D.

John H. Urabee, M.D.

Rehabilitation

Norvin C. Kiefer, M.D., *Chairman*
 A. Ray Dawson, M.D.
 N. Stanley Lincoln, M.D.
 William H. Roper, M.D.
 Thomas N. Sheen, M.D.
 Joseph B. Stocklen, M.D.
 Mr. Holland Hudson (NTA)
 Mrs. C. O. DeLaney (NCTS)

Medical Advisory Committee on Health Education

Arthur A. Pleyte, M.D., *Chairman*
 William H. Oatway, Jr., M.D.
 Olin S. Pettingill, M.D.

III. Medical Research and Therapy*Committee on Medical Research and Therapy (1) (2) (3) (4)*

Henry Stuart Willis, M.D., *Chairman*
 J. Burns Amberson, M.D.
 Charles A. Doan, M.D.
 Rene J. Dubos, M.D.
 H. Corwin Hinshaw, M.D.
 Esmond R. Long, M.D.
 Karl F. Meyer, M.D.
 H. McLeod Riggins, M.D.
 Florence R. Sabin, M.D.
 David T. Smith, M.D.
 Francis J. Weber, M.D.

- | | |
|--|---|
| <p>(1) <i>Laboratory Subcommittee</i>
 C. Eugene Woodruff, M.D., <i>Chairman</i>
 Martin Cummings, M.D.
 William H. Feldman, M.D.
 Max Lurie, M.D.
 C. Richard Smith, M.D.
 Charles R. Smith, M.D.</p> | <p>(3) <i>Chemotherapy Subcommittee</i>
 H. McLeod Riggins, M.D., <i>Chairman</i>
 J. Burns Amberson, M.D.
 Emil Bogen, M.D.
 Paul A. Bunn, M.D.
 H. Corwin Hinshaw, M.D.
 Kirby S. Howlett, Jr., M.D.
 Walsh McDermott, M.D.
 Edward N. Packard, M.D.
 Carroll E. Palmer, M.D.
 Arthur M. Walker, M.D.</p> |
| <p>(2) <i>Therapy Subcommittee</i>
 H. Corwin Hinshaw, M.D., <i>Chairman</i>
 John B. Barnwell, M.D.
 Robert G. Ferguson, M.D.
 Kirby S. Howlett, Jr., M.D.
 Daniel Jenkins, M.D.
 Richard H. Meade, Jr., M.D.</p> | <p>(4) <i>Laboratory Subcommittee on Chemotherapy</i>
 Guy P. Youmans, M.D., <i>Chairman</i>
 H. Corwin Hinshaw, M.D.
 C. Eugene Woodruff, M.D.
 Mr. William Steenken (NTA)</p> |

IV. Exchange of Scientific Information with Foreign Countries

(Committees to be appointed)

Latin America
Europe
Asia

V. Joint Committees

The Medical Section will be represented on committees of the U. S. Public Health Service, American Hospital Association, American Medical Association, Office of Vocational Rehabilitation, and the National Tuberculosis Association.

(The names of the committees and personnel will be announced later.)

AMERICAN TRUDEAU SOCIETY

Postgraduate Courses in Thoracic Diseases

The following postgraduate courses in thoracic diseases are being planned for the early part of 1948 by the American Trudeau Society, the Medical Section of the National Tuberculosis Association.

Under the auspices of nine regional committees, covering all States and Canada, the Society's program of postgraduate medical education is being carried out in cooperation with the medical schools of leading universities.

A subcommittee on continuation study of chest diseases for the general practitioner has recommended a pilot study for a national plan. The aim is to bring the general practitioner directly into contact with survey work, interpretation of X-ray films, and to assist him in the handling of cases in his area, and in his practice. Information concerning this course will be given in a subsequent issue of the REVIEW.

March 22-26, 1948 Region V (States of: Ohio, Indiana, Michigan, Illinois, Wisconsin, Missouri, Iowa and Minnesota)

American Trudeau Society in cooperation with the Detroit Department of Health and Wayne University College of Medicine, at Herman Kiefer Hospital, Detroit, Michigan. *Chairman:* Dr. Paul T. Chapman, Herman Kiefer Hospital. *Registration fee:* \$50.00.

March 22-27, 1948 Region III (States of: Maryland, Virginia, West Virginia, Kentucky, Tennessee, North Carolina, South Carolina, Georgia and Florida, and the District of Columbia)

American Trudeau Society in cooperation with the Medical Schools of the University of North Carolina and Duke University, at Chapel Hill and Durham, North Carolina. *Chairman:* Dr. H. Stuart Willis, North Carolina Sanatorium, McCain, North Carolina. *Registration fee:* \$50.00.

April 5-17, 1948 Region I (States of: Maine, Vermont, New Hampshire, Massachusetts, Connecticut and Rhode Island)

American Trudeau Society in cooperation with the Medical Schools of Harvard University, Tufts College and Boston University, at Boston, Massachusetts. *Chairman:* Dr. Theodore L. Badger, 264 Beacon Street, Boston, Massachusetts. *Registration fee:* \$100.00.

April 12-24, 1948 Region IV (States of: Alabama, Arkansas, Louisiana, Mississippi, Oklahoma and Texas)

Plans not yet completed. *Chairman:* Dr. Julius L. Wilson, Prytania and Aline Streets, New Orleans 15, Louisiana. *Registration fee:* \$100.00. Course to be held at Dallas, Texas.

NATIONAL TUBERCULOSIS ASSOCIATION

Exhibit at Annual Meeting in New York

Plans are being made for a scientific exhibit to be held in connection with the annual meeting of the National Tuberculosis Association at the Hotel Pennsylvania, New York, New York, June 15 to 18, 1948, according to an announcement by Dr. William H. Roper, Chairman of the Scientific Exhibit Committee.

Individuals interested in exhibiting material dealing with various aspects of tuberculosis and also nontuberculous pulmonary disease are invited to submit, not later than March 1, a preliminary description of the proposed exhibit. The description should be sent to Dr. William H. Roper, Director, Research Section, Army Medical Research and Development Board, P. O. Box 6027, Fitzsimons General Hospital, Denver 8, Colorado.

Because of space limitations, the Committee has stated it reserves the right to use its discretion in the final selection of material.

THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

ABST. No. 2

FEBRUARY, 1948

VOLUME LVII

Bronchial Stenosis.—Different aspects of pathogenesis and treatment of endobronchial stenosis are analyzed in three articles and illustrated by case histories. The first communication demonstrates the importance of bronchoscopic treatment: in a case of left pneumothorax with marked stenosis of the left main bronchus and endobronchial vegetations and ulcerations, bronchoscopic aspirations and topical applications of adrenalin were performed followed by monthly dilations with catheters of increasing caliber. Considerable improvement and enlargement of the bronchial lumen were observed on bronchoscopy, also confirmed by lipiodol studies. There was an increase in transparency of the previously opaque hemithorax. Concomitantly a marked clinical improvement was noted. The sputum became negative. This type of treatment has not provoked any complications in the above case as well as in similar cases. The second article gives the description of a progressive tuberculous stenosis of the trachea and both main bronchi in a case of cavitary disease of the left upper lobe, treated by thoracoplasty. Endobronchial treatment consisted in aspirations, adrenalin and silver nitrate applications following which the ulcerations healed. The local treatment was combined with the treatment of Charpy (40 injections of Sterogyl and 60 injections of calcium gluconate intravenously). There was, however, an increasing formation of fibro-sclerotic tissue leading to progressive ascending stenosis of marked degree. The third article gives examples of bronchial stenosis in childhood tuberculosis. A case of tuberculoma of the right main bronchus

with atelectasis of the right lower lobe and the right middle lobe is interpreted as a rare example of primary bronchial tuberculosis. In cases of epituberculosis the narrowing of the bronchial lumen was partly due to edema of the bronchial wall, partly to thick obstructing secretions. The rôle of enlarged tuberculous lymph nodes in the development of bronchostenosis and their perforation into the bronchial lumen is described.—*Intérêt des dilations dans les sténoses tuberculeuses des bronches souches*, P. Mounier-Kuhn & L. Meyer; *Évolution endoscopique d'une sténose trachéale progressive chez une tuberculeuse*, P. Mounier-Kuhn & L. Meyer; *Les sténoses bronchiques de la période primo-secondaire*, A. Dufourt & P. Mounier-Kuhn, *Rev. de la tuberc.*, 1947, 2: 64-72.—(V. Leites)

Ballooned Cavities.—Four cases are described in which ballooning of a cavity consecutive to pneumothorax and pneumonolysis was treated with intracavitary aspiration of air through the thoracoscope. In all cases endobronchial disease with bronchial narrowing was present. One or several aspirations of 30 to 50 cc. of air were performed with immediate effect on the size of the cavity. There was concomitant atelectasis of the corresponding lobe and development of a sero-fibrinous effusion. A few days after the intervention there was again some enlargement of the cavity in all cases, which, however, did not reach the initial size. Following this, all 4 cases showed progressive diminution and finally disappearance of the cavity within three to four months. Several hypotheses are advanced to explain the mechanism of this

therapeutic procedure when a check-valve type of bronchial stenosis was obviously responsible for the ballooning of the cavity. It is claimed that bronchoscopy consecutive to the intervention showed improvement of the bronchial involvement.—*Ponctions de cavernes soufflées sous pneumothorax. Quatre cas favorables, H. Despeignes, Rev. de la tuberc., 1947, 2: 747.*—(V. Leites)

Hemorrhagic Pleurisy.—While relatively common, the detection of a hemorrhagic pleural effusion does not usually settle the diagnosis. The experienced clinician may, however, use the coexistence of effusion and bleeding as the starting point for his deductions. No symptom is conclusive for differentiation before a puncture settles the matter. The presence of practically pure blood in the pleural cavity usually means malignancy or hemopneumothorax. Even an increased lymphocyte count does not rule out cancer. In neoplastic cases the course may be either insidious or accompanied by conspicuous symptoms, such as pain in the neck or arms, and pressure on adjacent organs without inflammatory phenomena. A small effusion with little fibrin, clotting tendency and hemolysis in the supernatant fluid also suggests cancer. Absence of sepsis is also corroborative. A number of conditions, including amebiasis, rheumatic disease, malaria, syphilis and pulmonary disease, may be present when an excess of eosinophils is present. If there is considerable respiratory difficulty, peripheral cyanosis, sensorial disturbances, high irregular fever and enlarged liver and spleen, miliary tuberculosis is a strong possibility, especially when the effusion is bilateral. Hemorrhagic pleural effusion is uncommon in chronic tuberculosis, it being more frequently an allergic manifestation in the secondary stage or associated with miliary tuberculosis. Argentine clinicians, in opposition to Norris' observations, find it but seldom in tuberculosis cases. The literature is exhaustively reviewed. One case of transitory hemorrhagic pleurisy in cancer, and 2 typical cases, one fatal, in tuberculosis, are reported

at length.—*Pleuresias hemorrágicas, S. Zabudovich, Prensa méd. argent., April 25, 1947, 34: 743.*—(A. A. Moll)

Treatment of Genital Tuberculosis.—Treatment of epididymal tuberculosis must be approached in the light of the new allergic conceptions. The degree of progressiveness must be determined, and the tuberculin test, X-ray studies, sedimentation rate, the Velez' and Arneith's indices and Schilling's count will help. If a progressive trend is apparent, a radical operation may prove dangerous, and the best policy seems to be watchful waiting in severe cases and a two-stage operation in milder ones. Actual epididymectomy is reserved for the second step. The first step, for which the writer claims credit, consists in an anastomosis of the deferent ducts which are attached through their sheath to the overlying inguinal skin. This preliminary procedure isolates the organs threatened from the infecting genital focus and furnishes a desirable physiological rest to the tissues.—*Tratamiento de la tuberculosis genital en el hombre, J. Lockhart, Prensa méd. argent., April 25, 1947, 34: 757.*—(A. A. Moll)

Hutinel's Disease in Mexico.—Four cases, 3 of them fatal, of enlarged liver with tuberculous pericarditis in children are described. They were all seen in the Children's Hospital in Mexico City between May, 1945 and October, 1946. Diagnosis is rather difficult as the onset is insidious and the modalities vary and sometimes the etiology is determined only by the necropsy findings. History, tuberculin tests, search for the tubercle bacillus, X-ray studies, tomography and cardio-electrography are, however, of real help. Prognosis is most serious and only in a few cases has surgery a chance, and this only in controlling the tuberculous infection. The patient still alive was to be treated with streptomycin before surgical measures were tried. Hutinel, however, described in his original report (1893) cases in which the disease had lasted several years. While tuberculosis is the most common cause, other factors may

also be responsible. For this reason and because of Pick's significant contribution, it is argued that the condition should be known as Hutinel-Pick's syndrome. In the Children's Hospital from its opening to August 31, 1946, there were 773 cases of tuberculosis among 15,678 admissions (4.93 per cent), meningitis (255 cases), pulmonary (239), bone-joint (127) and miliary types (28) heading the list.—*Tuberculosis cardiohepatica en el niño (síndrome de Hutinel-Pick)*, L. Berlanga Berumen, *Bol. méd. d. Hosp. inf., México*, March-April, 1947, 4: 184.—(A. A. Moll)

Miliary Tuberculosis with Heart Involvement.—In a 4-year-old boy, who had suffered from malaria when 2 years old, a diagnosis of pulmonary tuberculosis was made on entering the hospital. The condition progressed, with jaundice and finally meningitis developed and he died. The autopsy disclosed miliary involvement of both lungs, liver, spleen, bowel, meninges, and, most uncommon, heart and large blood vessels. Enlarged nodes filled the mediastinum and mesentery, two of these masses pressing upon the gall-ducts. A large node on the lower surface of the right lung was considered to be the primary focus. The tuberculous character of the lesions was confirmed by histological and bacteriological studies.—*Tuberculosis generalizada*, M. Salas, E. Contreras R. & J. Unda, *Bol. méd. d. Hosp. inf., México*, March-April, 1947, 4: 207.—(A. A. Moll)

Tuberculous Endocarditis.—A case of late primary pulmonary tuberculosis in a 26-year-old female, followed by generalized miliary tuberculosis, tuberculous endometritis and tuberculous endocarditis of the *chordae tendinae*, is described. There were no clinical signs of the endocarditis and the EKG was normal. The hematogenous dissemination occurred during the course of a pregnancy. The infant died of tuberculous pneumonia twenty-five days after birth.—*Über Endocarditis tuberculosa und kongenitale Lungen-tuberkulose*, M. Aufdermaur, *Schweiz. Ztschr. f. Tuberk.*, 1947, 4: 199.—(B. Gerstl)

Tuberculoma of Myocardium.—Myocardial tuberculosis occurs in three forms: (1) miliary, (2) nodular, (3) infiltrating. A 20-year-old colored man was seen who died with the signs and symptoms of chronic moderately advanced pulmonary tuberculosis with serofibrinous involvement of the left pleura and multiple cold abscesses. There were no symptoms or signs of a cardiovascular involvement. On autopsy, in addition to tuberculosis of lungs and other organs, there were found three tuberculous nodules in the left auricle: one was at the base of the mitral valve, 2 cm. in diameter, and two smaller ones were in the myocardium of the left atrium.—*Tuberculoma of the Myocardium: A Case Report*, S. M. Rauchwerger & R. J. Rogers, *Am. Heart J.*, August, 1947, 34: 280.—(G. C. Leiner)

Radiography in Tuberculosis of Esophagus.—On the basis of 2 cases verified by biopsy and autopsy, and 4 more reported in the literature, the roentgenographic changes produced by tuberculosis of the esophagus are described as those of ulceration, stenosing infiltration or tumor. Signs of ulcer and infiltration are more suggestive of tuberculosis but there is no characteristic pathognomonic X-ray change.—*Röntgenbefunde bei Oesophagus-tuberkulose*, M. Lüdén, *Schweiz. Ztschr. f. Tuberk.*, 1947, 4: 257.—(B. Gerstl)

Treatment of Lupus with Vitamin D2.—The authors briefly review the clinical manifestations and pathology of *lupus vulgaris*. They cite the work of Charpy who described the treatment of *lupus vulgaris* with vitamin D2. The technique is simple: vitamin D2, crystalline, in alcoholic solution, is given in dosage of 600,000 international units by mouth three times the first week, two times the week following, and once for the next three weeks. It is necessary that calcium be given in adequate amounts along with this treatment. They recommend 50 grains a day. The authors describe 2 cases of rather disfiguring *lupus vulgaris* which were considerably benefited by this treatment. They state that the treatment is simpler than other forms and

seems to be more efficacious.—*Lupus tuberculux et vitamine D2*, E. Gaumond & J. Grandbois, *Laval méd.*, June, 1947, 12: 571.—(A. T. Laird)

Tuberculous Adenopathy.—Case report of a 46-year-old male in whom casko-pneumonic tuberculosis with multiple cavitations in the right upper and middle lobe was associated with a right paratracheal adenopathy. There was evidence of a calcified primary complex in the right upper lobe. Bronchoscopy revealed a perforation of the caskous lymph node into the bronchial system, between the orifices of the right upper lobe and right middle lobe bronchi. The outcome was fatal. The particular interest of this observation is seen in the fact that the above findings, which are commonly encountered in primary tuberculosis, occurred here in a case of tuberculosis which was definitely of the reinfection type.—*Rupture endo-bronchique d'une adénopathie médiastinale de réinfection chez un sujet de 46 ans. Pneumonie nécrotique consécutive*, J. Brun, J. Viallier & Moindrot, *Rev. de la tuberc.*, 1947, 2: 762.—(V. Leites)

Labyrinthine Function in Streptomycin Therapy.—A series of 23 patients receiving streptomycin therapy for at least two months was studied for auditory and vestibular function. Fifteen patients were given 1.8 g. per day in divided doses every three hours, 8 received 2.0 g. daily; all subcutaneously administered. Audiometer tests were done every two weeks during the period of treatment; all but one of the 23 patients maintained a normal audiogram. The one exception was a demerol addict who showed a 65 db. loss for 3 tones: 2048, 4096 and 8192. She was an exceptional case in that she showed no caloric responses before, during or after 121 days of 1.8 g. of streptomycin per day. Almost all of the patients had vestibular signs and symptoms. One of the first symptoms was blurred vision while reading, appearing about the same time that a fine nystagmus with lateral gaze in either direction could be detected. Vertigo usually began in the third

or fourth week of treatment, varying in onset from eleven to sixty days in 17 patients. Although subjective vertigo lasted one to two weeks in most patients, vestibular function tests showed persistent abnormalities. All but 3 of the patients developed loss of reaction to rotation and caloric stimulation when treatment was continued for more than twenty-five days. The gait of 6 ambulatory patients showed a broad base and some ataxia after three to four weeks of treatment but compensation gradually took place so that in four months incapacity was not perceptible if vision were unobstructed and the walking surface smooth. Unsteadiness was revealed in walking on graded slopes or with vision obstructed. Walking was almost impossible in the interval between the beginning of a changed response to caloric stimulation and final occurrence of a negative response. Three months after the negative response first occurred, they did quite well under ordinary conditions. It was noted that patients over 60 showed less ability to compensate in walking, although the younger patient did very well. No recovery of response to caloric stimulation has been observed up to four months after cessation of therapy in these patients. Rotation tests showed no effect on patients who received the streptomycin, in contrast to normal subjects who show nystagmus, past pointing and ataxia after rotation. Tilting the affected patients on a table showed delayed response to changes in position. Localization of the lesion is still conjectural in streptomycin treated patients. Loss of rotation and caloric response with tiltable response being of the peripheral type suggest a labyrinthine lesion. So far, there is no convincing pathological evidence that this assumption is correct.—*Tests for Labyrinthine Function following Streptomycin Therapy*, A. Glorig & E. P. Fowler, *Ann. Otol., Rhin. & Laryng.*, June, 1947, 56: 379.—(P. Q. Edwards)

Antibiotic Clitocybine.—Studies were made on the antibiotic properties of substances present in the mycelia and carpophores of

the mushroom *Clitocyba candida*. The mushroom grows in the French and Swiss Alps. It forms characteristic, indented circles, called "witches' circles," with patches of dead plants, killed by the mushroom. The fact that these plants remained well preserved for a long period indicated the presence of an antibiotic agent (the author prefers the term "abiotic"). For experiments *in vitro*, the following method was employed: Appropriate nutritive media were inoculated with the microorganism to be tested, and poured into Petri dishes. Pieces of the mycelium or morsels of blotting paper soaked with varying concentrations of the extract were placed upon the surface of the Petri dishes and incubated. Clear areas formed around the morsels which were devoid of microorganisms. One of the extracted substances, Clitocybine B, showed some specific action against the Koch bacillus. Such bacilli, previously brought into contact with the antibiotic substance and then transferred on suitable media, showed an extremely delayed growth. Experiments *in vivo* were carried out on guinea pigs. The animals were inoculated with tubercle bacilli and afterwards treated with daily subcutaneous injections of the extract. Circumscribed, pulmonary lesions developed with characteristic, histological features, as scant caseation, absence of epithelioid and lymphoid cells, abundance of polynuclear leucocytes. Tubercle bacilli were either completely absent or they formed agglomerated, ill defined masses. In such cases, the leucocytes also contained numerous, phagocytosed tubercle bacilli. The author concludes from these findings that the substance not only inhibits the growth but also causes lysis of the bacilli and prevents them from elaborating their cytotoxic products, so that they may be acted upon and phagocytosed by the leucocytes. The author has succeeded in culturing the mycelia on Sabouraud's media and in obtaining crystallized and more purified extracts, with which extensive experiments are now being carried out.—*La Clitocybine et le bacille tuberculeux*, C. Hollande, *Méd. Digest, Bruxelles*, No. 5, May, 1947.—(E. C. Frey)

Tuberculin Sensitivity.—Recently, Chase was successful in transferring tuberculin sensitivity passively by injecting cells from peritoneal exudates of tuberculin-sensitive guinea pigs into normal guinea pigs. Freund, Valtis, and Valtez and Saenz found a difference in the intensity of the tuberculin test in very young and old guinea pigs actively sensitized by infection. An attempt to duplicate Chase's studies and to determine whether the age of the animals has a pronounced influence on the passive transfer of sensitivity is reported in this paper. The method of sensitizing 22 guinea pigs approximately 132 weeks old, and 33 guinea pigs 3 weeks old and the tuberculin tests performed four weeks later are described in detail, as well as the method of obtaining peritoneal exudate cells from the animals and inoculating measured volumes of these cells peritoneally into normal animals. Twenty-four and forty-eight hours after inoculation, the recipients were tested intracutaneously with dialyzed Old Tuberculin. The skin reactions were measured twenty-four and forty-eight hours following the test injections. Control injections with the peritoneal exudates obtained from 10 young and 3 old not sensitized guinea pigs were given to 5 normal young animals, and they were tested like the experimental animals. In 3 cases slight, transient reactions to a 1:40 dilution of tuberculin were found which disappeared before the end of forty-eight hours; therefore, only forty-eight hour readings were considered reliable. Characteristic tuberculin reactions were obtained in 7 of the 10 animals which received peritoneal exudates from sensitized guinea pigs. No reactions occurred in animals treated with exudates from normal guinea pigs. Thus, the work of Chase was confirmed. However, reactions of approximately the same size were elicited in both young and old recipient animals; passive transfer of sensitivity did not appear to be greatly influenced by the age of the donor or the recipient animals.—*Passive Transfer of Tuberculin Sensitivity in the Guinea Pig*, M. M. Cummings, Martha Hoyt & R. Y.

Gottshall, *Pub. Health Rep.*, July 4, 1947,
62: 994.—(O. Pinner)

ABSTRACTS

Tuberculin Sensitivity.—Mode of administration of tubercle bacilli as a factor in production of allergy in animals has been studied in an effort to obtain further information regarding the phenomenon of skin sensitivity to tuberculin. Bovine bacilli, Dupray strain, of known virulence were used in doses of 0.1 mg. Tuberculin tests were made by intracutaneous injection of standard Pasteur Institute product diluted 1:10. Only animals surviving long enough for adequate testing of sensitivity were included in the report: a total of 51 guinea pigs. Subcutaneous inoculation of 15 animals resulted in the classical local lesion by the twelfth day. All reacted to tuberculin by the fifteenth day. This reaction followed the well-known process of progressively augmented intensity. The animals died by the thirty-eighth to sixty-fourth day with classical lesions. This group may be considered as controls. Only 2 guinea pigs received intramuscular injections; both had positive tuberculin reactions by the fifteenth day; both died with gross visceral lesions within two months. Twenty-four animals received intratesticular injections which produced acute orchitis within fifteen days. All died between fifteen to forty-six days with very acute peritoneal and visceral lesions. However, these animals showed no reaction to tuberculin on repeated injections between the thirteenth and thirty-seventh days. A few of these animals showed very slight thickening of the skin at the injection site, but the reaction was not considered positive. Four animals infected intratracheally died between the twenty-first and fortieth day; 3 among them had no reaction to tuberculin on the seventeenth and twenty-third days; one reacted positively on the same days. This animal had a local lesion at the site of injection. Intravenous inoculation of 6 animals with minute doses of bacilli caused death without showing any reaction to tuberculin in thirteen to twenty-eight days. Two guinea pigs infected intraperitoneally died in thirty

days with negative tuberculin reactions. This study indicated that sensitization of the skin to tuberculin results after inoculation of bacilli in the skin and muscle only. Perhaps because of the rapid progress of the disease induced by other routes of inoculation the animals lost their ability to react, although many tests were made several weeks before death with negative reactions. Apparently a tegumentary lesion plays an important rôle in producing allergic sensitivity when one seeks to demonstrate such allergy by cutaneous reactions.—*Influence sur l'apparition de l'allergie cutanée chez le cobaye de la voie d'inoculation des bacilles tuberculeux*, P. Gastinel & A. Nivol, *Ann. Inst. Pasteur*, May, 1947, 73: 485.—(P. Q. Edwards)

Tuberculin Tests.—Almost all persons giving a negative reaction to an adequate tuberculin test are free from clinical tuberculosis. Infrequently, a negative reactor may prove to be infected or rarely to be a clinical case. A few negative reactions are due to waning of skin sensitivity with passage of time in obsolete cases of infection. Nonreactors are sufficiently numerous to make the test of practical value in children and young adults.—*The Significance of the Negative Tuberculin Test*, B. Couss, *Brit. J. Tuberc.*, April, 1947, 41: 42.—(A. G. Cohen)

Weltmann Reaction.—The laboratory findings of 100 cases of pulmonary tuberculosis were correlated to clinical observations and course of the disease. Out of 82 cases with a slightly to moderately shortened coagulation band (Weltmann), 20 died, the remaining 62 improved. All but one of the 18 cases with elongated coagulation band became clinically arrested. The sedimentation rate was the most sensitive indicator for the degree of activity of the disease. The results of the Takata reaction were irregular and failed to show any correlation with course and clinical signs. Thus, sedimentation rate and Weltmann nephelogram are the tests best suited to assist the clinician in prognosticating pulmonary tuberculosis.—*Zur Humoralpatho-*

logie der Lungentuberkulose, A. Pedrazzini, Schweiz. Ztschr. f. Tuberk., 1947, 4: 274.—(B. Gerstl)

Calcification and Skin Sensitivity.—An attempt has been made to solve the etiology of pulmonary calcifications, using the subjects and data of the Fels Research Institute in southwestern Ohio. Two hundred "normal" children have been studied from birth by means of serial X-ray films (each six months for two years, yearly thereafter), and 170 have had skin tests with tuberculin, histoplasmin and other antigens. It is known that 25 to 83 per cent of young persons, living chiefly on the eastern slope of the Mississippi River basin, show calcification in X-ray films; less than half react to tuberculin, but the non-reactors are often sensitive to histoplasmin. In the present survey, the 170 children were all one year of age or older (45 were less than 5 years of age, 53 were from 5 to 9, 50 were from 10 to 14, and 22 were from 15 to 19 years). The skin-test routine consisted of the usual two strengths of PPD, a single dose of 1:1,000 histoplasmin, and, if these were all negative, tests with 1:1,000 blastomycin and haplosporin. One hundred and three children (60.6 per cent) showed intrathoracic calcification. Tuberculin tests were positive in 15.3 per cent of the entire group; histoplasmin tests were positive in 44.7 per cent. Eighteen children reacted to both tests, 15 having calcifications; 8 reacted only to tuberculin, 6 having calcifications; 58 reacted only to histoplasmin, 49 having calcifications; 86 were negative to both, but 33 had calcifications. Of the 33 children negative to the routine tests, only 2 reacted to blastomycin, and one of these also reacted to haplosporin. Previous tuberculin tests indicate that the positives and negatives have remained constant in spite of the presence of calcification. The study has allowed X-ray and skin-test surveys of relatives of the children; there has been a tendency to family distribution of calcification, but not of histoplasmin sensitivity. In summary, more children were sensitive to histoplasmin than tuberculin;

the incidence of pulmonary calcification is more closely associated with histoplasmin sensitivity than tuberculin reaction; and there is a much closer association between the onset of calcification and histoplasmin sensitivity than with tuberculin sensitivity. Most of the children with calcifications showed soft tissue changes by roentgenogram before 48 months of age, consisting of infiltrates and round areas of consolidation. New lesions continued to appear and calcify in children with positive histoplasmin tests.—*Lung Calcifications and Histoplasmin-Tuberculin Skin Sensitivity*, L. W. Sontag & J. E. Allen, J. Pediat., June, 1947, 30: 657.—(W. H. Oatway, Jr.)

Inhibition of Mycobacterium.—The author added varying concentrations of monoalkyl and dialkyl succinic acids and monoesters and monoamido-derivatives of alkyl succinic acids to a nutrient peptone digest broth which in some cases was enriched with 5 per cent pooled human serum. The medium was inoculated with either *M. smegmatis*, *M. tuberculosis bovis* 46 or *M. tuberculosis hominis* H37RV. Final readings of the growth of *M. smegmatis* were taken on the sixth day and of *M. tuberculosis bovis* or *hominis* on the forty-second day of incubation and compared with the controls. The chemicals were also tested for hemolytic action on standard suspensions of washed human erythrocytes at 37° C. for one hour. It is concluded that some of the new series of compounds markedly inhibit the growth of *M. tuberculosis*. The antibacterial and hemolytic action was most marked when the combined constituents of the compounds contain 13 or 14 carbon atoms. The antibacterial action is bactericidal. The addition of serum albumin to the compounds reduces the antibacterial and hemolytic action.—*The Action of Monoalkyl and Dialkyl Succinic Acids and the Monoesters and Monoamido-Derivatives of Alkyl Succinic Acids on the Growth of Mycobacterium Tuberculosis*, P. A. McNally, Brit. J. Exper. Path., June, 1947, 28: 211.—(H. J. Henderson)

Friedmann's Vaccine in Genital Tuberculosis.—A 16-year-old girl was operated upon for tuberculous oophoro-salpingitis and afterwards received one dose of Friedmann's vaccine subcutaneously. This seemed to result in immediate and visible improvement of her general and local conditions. However, two months later she lost weight rapidly and experienced severe pain in her left lung. A soft infiltration was found in the left infraclavicular and basal regions and collapse therapy was started. The author points out that all surgical localizations of tuberculosis are secondary to a pulmonary lesion, sometimes undetectable in its beginnings. The follow-up of gynecological cases of tuberculosis treated with Friedmann's vaccine has not shown sufficient success to warrant the enthusiasm of certain gynecologists for his treatment. [It would seem that the inefficacy of treatment with Friedmann's vaccine was well established a good many years ago. —Editor]—*A propósito de un caso de tuberculosis genital tratada con vacuna a germenes vivos*, R. Burgos, *Hoja fisiol.*, December, 1946, 6: 477.—(W. Swienty)

BCG Vaccination.—This is an evaluation of present data on the efficacy of BCG in the prevention of tuberculosis. The safety of BCG in man is accepted on the basis of the experience with over 5,000,000 inoculations. However, there are numerous favorable reports on the efficacy of BCG vaccine taken severely to task, because many of them have been inadequately controlled. This criticism certainly does not apply to the work of Aronson on the protection of American Indians by BCG. Practically all the criteria set down by Levine for a searching investigation into the efficiency of the vaccine have been scrupulously fulfilled by Aronson and his associates, including the all important alternating of individuals for vaccination and control. Unfortunately, Levine is under the misapprehension that this was not done in the Indian study. Levine has been influenced in his skepticism on efficiency of BCG by the absence of decisive data in his own experience in

New York. Whether this is due to the very low incidence of tuberculosis among these children and hence, under the circumstances, to a very limited experience, remains to be determined. Despite these criticisms, which in some instances are well taken, Levine concedes that the BCG affords a certain degree of protection. He therefore urges continued research in BCG vaccination, especially in relation to the duration of the immunity afforded, the significance of tuberculin sensitivity following vaccination, the efficacy of the vaccine in different racial groups and the relative potency of the BCG when prepared under different conditions.—*Evaluation of the Use of BCG in the Prevention of Tuberculosis in Infants and Children*, M. I. Levine, *Am. J. Pub. Health*, September, 1947, 37: 1096.—(M. B. Lurie)

BCG Vaccination.—In a rather long address at Brussels on December 5, 1946, before the Belgian Society for the Scientific Study of Tuberculosis and Pneumology, Guérin, co-worker of Calmette in the development of BCG, summarizes his views of the value of his vaccine. If postnatal exposure takes place within the first three months of life, the mortality is nearly 100 per cent; if within the first year and one-half, 30 per cent. As children become older their resistance to tuberculosis increases for two reasons: their bodies have developed greater natural resistance and they have acquired a degree of specific resistance through occasional contact with tubercle bacilli not too numerous or too virulent. Many persons do not come in contact with tubercle bacilli and secure spontaneous resistance until adolescence. This is particularly true of children who grow up in the country and later come to the city to work. Recruits for the Army from the country are in the same category. Many of these persons are as readily infected as infants, and have as a result of this infection a rapidly progressive form of tuberculosis. The one means that, according to the present state of our knowledge, has proven of value is the introduction into the body of living tubercle bacilli, which

however should have no power of doing harm to the individual who receives them. The Pasteur Institute at Lille had in 1908 a strain of tubercle bacilli of marked virulence. Calmette and Guérin cultured it on strongly alkaline glycerinated-bile potato medium and made transplants every fifteen days. It became less and less virulent and after thirteen years, that is after 230 transplantations, it had lost all capacity of provoking the formation of reinoculable tubercles. After tests on some hundreds of thousands of young calves and other animals, it was found that it had retained its power of vaccinating against later infections with virulent tubercle bacilli. Vaccination with BCG was first applied to human beings in 1921. Since that time, according to Guérin, over a million individuals have been vaccinated in France and many thousands elsewhere. Twenty-five years have passed and it is now possible to assert that it is not at all dangerous and that it is effective. The technique of vaccination by scarification, which is similar to that of smallpox vaccination, has come into wide use and is given in some detail. BCG is an attenuated strain of tubercle bacilli which has become stabilized and which will not produce progressive disease. It may therefore, if properly administered, be considered harmless. This paper by one of the originators of BCG vaccination is interesting and well worth reading.—*La vaccination par le B.C.G., C. Guérin, Rev. belge de la tuberc., 1947, 38: 1.*—(A. T. Laird)

Electrokymography.—Roentgen kymography was invented by Sabat in 1911. This procedure is the roentgen demonstration of the movements of the diaphragm, heart and aorta. The apparatus was simple, consisting of a single slit diaphragm. In 1928, Sturup introduced the grid with multiple parallel slits replacing the diaphragm. Hirsh, in 1934, devised a system permitting synchronization of the kymographic tracing with the electrocardiographic tracing. In 1942, Morgan invented the phototimer, a remarkable instrument capable of automatically controlling the time of exposure in roentgenography under

various conditions. Chamberlain, Henny and Boone combined the photoelectric pick-up of heart movements with an electrocardiographic type of registration to make a new instrument, the roentgen elektokymograph. This instrument has obvious technical advantages over ordinary roentgen kymography. It will soon prove its usefulness in the examination of many hitherto undiagnosable conditions of the cardiovascular system.—*Roentgen Kymography and Roentgen Elektokymography, T. Leucutia, Editorial, Am. J. Roentgenol., May, 1947, 57: 629.*—(J. E. Farber)

Breath-holding Time.—In 341 determinations with the subjects at rest at ground level (altitude 500 feet) breathing air, the breath-holding time was 34 to 125 seconds, with an average of seventy seconds. Hyperventilation and oxygen inhalation increase the breath-holding time. It decreased with increasing altitude and following exercise. The average breath-holding time during escape from a spinning centrifuge, imitating the conditions of spinning aircraft, was seventeen seconds.—*The Effect of Oxygen, Altitude and Exercise on Breath-Holding Time, S. Rodbard, Am. J. Physiol., July, 1947, 150: 142.*—(G. C. Leiner)

Respiratory Volumes of Laboratory Animals.—Several methods of determining the respiratory volume, including the oscillographic respiograph, have been presented. Data on quiet respiration in 428 animals of 8 species have been presented. The data presented indicate that the respiratory volume varies directly neither with the weight of the body nor with the body surface but approximately with the $\frac{2}{3}$ power of the weight. A formula has been derived for the determination of respiratory volume of an animal provided the weight is known. (Author's Summary.)—*Measurement of the Respiratory Volumes of Laboratory Animals, A. C. Guyton, Am. J. Physiol., July, 1947, 150: 70.*—(G. C. Leiner)

Respiratory Patterns in Laboratory Animals.—Respiratory patterns of mice, cotton

rats, hamsters, white rats, guinea pigs, rabbits, monkeys, dogs and men have been illustrated and analyzed. In general, the respiratory pattern varies little between one species of animals and another except for rate and tidal air. Within any one species of the smaller animals, the respiratory pattern is relatively constant. Formulae based on weight have been derived for tidal air, rate of flow, inspiratory and expiratory rate of breathing, inspiratory and expiratory speed of flow, pressure drop in the trachea, and retention of particles within the nasal passages. In general, the calculated values from these formulae agreed within 20 per cent of those which could be measured. Considering the great number of variables in respiratory dynamics, this agreement is considered to be reasonable. As an example of information which can be gained from respiratory patterns, two experiments on the anesthetization of rabbits with nembutal are presented. (Author's Summary.)—*Analysis of Respiratory Patterns in Laboratory Animals*, A. C. Guyton, *Am. J. Physiol.*, July, 1947, 150: 78.—(G. C. Leiner)

Absorption from Pulmonary Alveoli.—Any material absorbed from a normal lung alveolus must pass through its epithelial lining and penetrate the walls of the alveolar blood and lymph capillaries. From the small surface area available and the anatomical barriers imposed, bronchiolar absorption is of little importance compared with the absorption from the alveoli. Experiments were done on dogs, anesthetized with nembutal, in which lung lymph, thoracic duct lymph, and blood specimens were separately collected after intratracheal introduction of the test materials. Nearly all the lymph from a dog's lung enters the blood through the right lymphatic duct. Despite the fact that connections between this duct and the thoracic duct are frequent, in a certain number of animals the right lymphatic duct can be individually cannulated and will deliver no lymph save from the heart and lungs. The presence of the test material in the blood

(and thoracic duct lymph) would be an indication of alveolar blood capillary absorption. The instillation of a 1 per cent solution of T-1824 (a blue dye) in physiological salt solution introduced into the trachea of a dog showed a fairly rapid appearance of the dye in the lung lymph and the blood. As there was no possibility of lymphatic delivery of dye into the blood, molecules of the dye must have directly entered the blood. In contrast to the ready absorption of T-1824 in water, certain experiments were done in which the dye was combined with proteins such as dog plasma and crystallized egg albumen. The absorption of these proteins was slight. Also purified bovine serum albumen was tested and examined by a precipitation method. Its absorption was also slight. When hemoglobin was introduced into the trachea its absorption could not be detected. Experiments in which pyrex glass spheres averaging 4 micra in diameter were instilled failed to disclose entrance of these distinctive foreign particles in the lymph stream during the test flow of lung lymph. Intact alveolar epithelium apparently permits only very slight absorption of proteins commonly entering the pulmonary alveoli as a result of trauma or disease. (With 1 plate.)—*Absorption from the Pulmonary Alveoli*, C. K. Drinker & E. Hardenbergh, *J. Exper. Med.*, July, 1947, 86: 7.—(J. S. Woolley)

Pulmonary Function for Silicosis.—The author calls attention to the discrepancy of roentgenographic appearance of pulmonary silicosis and the results of pulmonary function tests. Frequently, patients showing slight fibrosis and nodulation reveal severe damage on function tests, while others with advanced changes on X-ray examination show a function better than expected. The former may be due to bronchial spasms, superimposed infection, cardiovascular diseases or aggravation. The latter may be explained on the basis of adjustment to the gradually developing reduction of respiratory epithelium. Simple function tests, such as spirometry, expansion of thorax and voluntary inspiratory and expiratory apnea are considered sufficient.—*Die*

Leistungsprüfung bei der Beurteilung von Silikolikern, F. Lang, Schweiz. Ztschr. f. Tuberk., 1947, 4: 257.—(B. Gerstl)

Calculation of Dead Space.—The dead space was calculated according to Rossier's formula

$$DS = \frac{\text{Minute volume in cc.} - \text{alveolar ventilation in cc./Frequency of respiration per minute}}{\text{per minute}}$$

with and without adding an artificial dead space of 100 cc. It averaged 173.7 cc. The maximum deviation from the added 100 cc. dead space were -33 and +41 cc. The fact that a hyperventilation of +21 per cent, in presence of the artificially superimposed dead space, did not increase alveolar ventilation nor produce alkalosis of the arterial blood, suggests that the increase of minute volume is due to hyperventilation of the dead space. This hyperventilation can be prevented by bandaging the thorax tightly. It resulted in increased carbon dioxide tension of the arterial plasma, slight acidosis and a 16 per cent decrease of alveolar ventilation. The condition simulated that observed in cases of emphysema with rigid thorax, pulmonary tuberculosis, etc. The magnitude of the physiological dead space was conversely proportional to frequency of respiration, and directly proportional to respiratory volume. The dead space can be calculated according to Rossier's formula from frequency of respirations and minute volume, only if the alveolar ventilation is assumed to be constant. The correctness of this assumption is tested by determining carbon dioxide and oxygen in the arterial blood. The combination of such procedures with spirometry is therefore essential for estimating the physiological dead space.—*Totraum und Totraum-hyperventilation, E. Blickenstorfer, Schweiz. Ztschr. f. Tuberk., 1947, 4: 59.—(B. Gerstl)*

Pulmonary Insufficiency and Oxygen Deficit.—A double spirometer was devised permitting instant switching from pure oxygen to air containing various but constant concentrations of oxygen. Registration on the kymograph was synchronized with each spirometer and could

be continued for fifteen minutes. The minute volume was calculated from the diagrams obtained. Arterial blood samples were analyzed for oxygen and carbon dioxide. The additional uptake of oxygen upon breathing pure oxygen was small and dyspneic patients varied in their mean respiration. These factors rendered interpretation of the kymographic charts difficult. Some of the patients with respiratory insufficiency did take up additional oxygen under oxygen respiration but there was no correlation between the oxygen deficit of arterial blood and the amount of additional oxygen absorbed, or the minute volume. The quantity of oxygen taken up by normal individuals remained constant whether air or oxygen was breathed. Thus, spirometry cannot replace the determination of oxygen of the arterial blood. The large differences of oxygen uptake by cases with pulmonary insufficiency remain unexplained.—*Über das sogenannte Sauerstoff-Defizit nach Uhlenbruch-Knipping, G. Nager, Schweiz. Ztschr. f. Tuberk., 1947, 4: 1.—(B. Gerstl)*

New Resuscitator.—The terms used in America and England to describe treatment for asphyxia are defined. The two general types of resuscitation are discussed, the *manual* methods, requiring no equipment, and including mouth-to-mouth insufflation and the various posture and manipulation procedures, and the *mechanical equipment* methods, including transpharyngeal insufflators, endotracheal insufflators, inhalators, extrapulmonary differential pressure devices, positive-negative pressure devices, the intermittent positive-pressure devices and the rocking table. Simplicity and the use of oxygen are points favorable to a method; reliance on the elastic recoil of the chest, and the use of negative pressure intratracheally are disadvantages. The Burns PBR (Pneumatic Balance Resuscitator), or the "baby lung," is a new type of intermittent positive-pressure apparatus. The PBR valve was designed at the Aero Medical Laboratory, Wright Field. The equipment consists of a mask and an automatic valve through which the oxygen supply flows from a regulator and

source of supply. Any type of closely-fitting mask may be used. The valve contains channels and diaphragms, which allow the valve to "cycle" between the pressure in the mask and the pressure of the oxygen regulator. A rising line-pressure will close the valve; a rising mask-pressure will open the exit ports to the outside. Use of the PBR on subjects in deep coma and freshly dead is reported, as well as the effects of PBR on pulmonary ventilation, blood gas and pH content in a series of patients. The valve works well over long periods of time and in spite of secretions. PBR failed in its original purpose in aircraft, but it has several interesting clinical uses. It has been used to shorten the period of unconsciousness after general anesthesia; in narcotic intoxication with a low respiratory rate; and as an adjunct to a Drinker respirator in case of power failure or during transfer. It may also be of value in cases of cardiac failure, since use of the valve results in a decreased venous return to the heart—a result similar to that of venesection and peripheral tourniquets. PBR may be of considerable use to the clinician.—*Artificial Respiration and the Pneumatic Balance Resuscitator*, H. J. Jacobs, *Bull. U. S. Army M. Dept.*, August, 1947, 7: 707.—(W. H. Oatway, Jr.)

Interlobar Fissures.—Variations of interlobar fissures of the lungs were studied in 1,200 consecutive autopsies. A complete fissure was found in 82 per cent in the left lungs, a major fissure in 70 per cent in the right lungs and a middle lobe fissure in 38 per cent in the right lung.—*Variations in Interlobar Fissures*, E. M. Medlar, *Am. J. Roentgenol.*, June, 1947, 57: 723.—(J. E. Farber)

Agenesis of Lung.—The term "agenesis" should be restricted to those cases with no development of the lung, and "aplasia" should be used for those with incomplete development (as suggested by Schneider). Since the advent of bronchoscopy, the diagnosis is made more often in living patients. A total of 54 cases have previously been reported, to which one case is added. A Negro infant, aged 2 months,

was admitted to the hospital in respiratory distress and in poor general condition. There was consolidation, lack of aeration and narrowed interspaces on the left. Death occurred in twenty-four hours. Necropsy showed agenesis of the left lung; agenesis of the apical lobe and eparterial bronchus on the right; absence of the left pulmonary artery; edema and congestion of the right middle lobe; atelectasis of the right lower lobe; a patent ductus arteriosus and foramen ovale; cor pulmonale, and displacement of the heart to the left; and an inguinal hernia on the left. The embryology and diagnosis are discussed, and 11 recent cases are tabulated.—*Agenesis of the Lung: With a Review of the Literature*, R. A. Burger, *Am. J. Dis. Child.*, April, 1947, 73: 481.—(W. H. Oatway, Jr.)

Spontaneous Pneumothorax in Sarcoidosis.—A case of sarcoidosis verified by biopsy in which a spontaneous pneumothorax occurred is reported. The course of the disease remained benign and the pneumothorax was resorbed without further therapy.—*Spontanpneumothorax bei der Besnier-Boeck-Schaumann'schen Krankheit*, M. Dressler, *Schweiz. Ztschr. f. Tuberk.*, 1947, 4: 229.—(B. Gerstl)

Carcinoma of Lung.—Symptoms and signs of carcinoma of the lung depend upon the relationship of the growth to the thoracic organs, particularly the pressure effects upon the lung and bronchi. Complete obstruction of the large bronchi, usually by squamous cell carcinoma, results in atelectasis. Incomplete obstruction results in suppuration with or without lung abscess. There may also be breakdown within the tumor itself, in which case the abscess is not segmental, is radiologically eccentric to the main shadow and may have an irregular outline. Invasion of the pleura results in pain or discomfort and effusion. The fluid may be clear, bloody or purulent and may or may not contain tumor cells. Interference with the mediastinal tissue is due to glandular involvement; this is seen in the oat cell or undifferentiated types. The great veins may be obstructed and there may be paralysis of the

phrenic or recurrent laryngeal nerves. The heart is invaded sometimes. Glandular metastases are common in the oat cell type where the lymph nodes are heavily involved; surgery is impracticable in these cases. Regional metastases are less common in squamous cell and adenocarcinoma. In these, secondary deposits may develop with predilection for bone (ribs and vertebrae), liver, skin, brain and adrenals. The early symptoms of significance are: (1) appearance or change in the character of the cough in middle-aged or older persons, (2) hemoptysis and (3) dyspnea and transitory wheezing. Pleuritic pain and osteoarthropathy are also significant. The most important diagnostic procedures are X-ray, bronchoscopy and identification of cancer cells in the sputum. Oat cell carcinomata with regional metastases are inoperable. Squamous cell carcinomata giving early atelectasis are often removable. Pleural effusion, glandular involvement, infiltration of the phrenic and vagus nerves and extension to the diaphragm or chest wall, while not absolute contraindications, make success doubtful. The proportion of suitable cases is very low. In the authors' series the chest was opened in 246 cases; resection was possible in 130 (122 pneumonectomies and 8 lobectomies). There were operative deaths in 15 per cent. Postoperatively the most important consideration was the behavior of the vacant space. If no infection occurred, there was slow obliteration in a few months with increasing deposit of fibrin. Some patients later required a thoracoplasty.—*Carcinoma of the Lung*, T. H. Sellors, G. Cruickshank & B. R. Billimoria, *Lancet*, July 26, 1947, 2: 119.—(A. G. Cohen)

Resection for Neoplasm of Lung.—A detailed analysis has been made of the fate of 360 patients with primary pulmonary malignancy seen in the eleven years between January, 1936 and December, 1946. Twenty-eight per cent occurred in private practice, 16 per cent of which came to pulmonary resection; 72 per cent were seen in a charity hospital, 43 per cent of which had resection—a total of 129 resections. Compared with the stable occurrence

of carcinoma of the stomach, there seems to be a slight yearly increase in the incidence of primary carcinoma of the lung. No reason (such as occupation or smoking) was found for this increase. The condition is twice as common in whites as in Negroes, and more than four-fifths of all patients were males. By far the greatest number were between 40 and 70 years of age, with the greatest incidence in the fifth decade. The insidious onset and the vague clinical picture account for the frequent delay in diagnosis. The common sites of involvement have been listed, but the pathology is to be reported later. The mortality without surgery is considered to be 100 per cent. Of the 360 cases, 109 were considered to be inoperable and 41 refused surgery—a total of 150 (42 per cent); 251 (70 per cent) were considered operable, and 210 were explored; 81 cases (22 per cent) were nonresectable, and 129 cases (36 per cent) were resected. Fourteen of those explored but not resected died in the hospital; 32 of those resected (24.8 per cent) died in the hospital. Forty-five patients were alive from six months to five years after resection—a range of 54 to 22 per cent of those resected. A person who lives three years after resection usually is alive at five years. Extensive charts are shown to illustrate the various rates and their modifying factors. It is suggested that routine roentgenological examination of the chest is the most valuable diagnostic method. It should be supplemented where indicated by bronchography, bronchoscopy, biopsy and study of bronchial secretions.—*Primary Pulmonary Malignancy Treated by Resection*, A. Ochsner, M. de Bakey & L. Dixon, *Ann. Surg.*, May, 1947, 125: 522.—(W. H. Oatway, Jr.)

Surgery for Carcinoma of Lung.—The first pneumonectomy was done thirteen years ago at Johns Hopkins Hospital. Diagnosis of primary pulmonary carcinoma was rare at that time. Medical and radiation therapy was and is ineffective. A series of 327 consecutive cases seen during the thirteen years is presented, and the data are analyzed. The majority of patients is in the fourth to sixth decades. A high proportion (6 to 1) were

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males, a possible result of the exposure of that sex to chronic irritations of the lungs and its resultant stimulation of abnormal cell growth. There are no pathognomonic signs or symptoms, but an unusual and persistent cough or an unexplained hemoptysis is suggestive. The X-ray film showed lesions in 100 per cent of the cases. Exploratory thoracotomy is the final diagnostic method, and should be used more freely. The majority of the cases in this series were near the hilum; they either arose from the mucosa and grew into the bronchus (centripetally), or arose from a small bronchus and grew extrabronchially along or around the bronchus. The symptoms depend considerably on the method of growth. Sixty-five per cent were flat, or squamous cell carcinomata; 35 per cent were adenocarcinomata. In general, the patients with squamous cell type lived longer after excision. A total of 215 cases (66 per cent) was inoperable, by reason of pleural or distant metastases. Pneumonectomy was the only type of operation used, and it was done in 112 cases. Seventy per cent had metastases in the bronchial or tracheobronchial nodes. The preoperative preparation, using penicillin and pneumothorax, is described, as is the operative procedure. The immediate postoperative mortality, including all deaths during the first month, has been 22 per cent (27 per cent from 1933 through 1939, 17 per cent from 1940 through half of 1946). Forty-four cases (39 per cent of those resected) survived the operative period but are now dead. Forty-three cases (39 per cent of those resected, 13 per cent of the entire series) have lived from one month to thirteen years. The average duration of life of the 215 cases which were nonoperable was five months. Most patients have been rehabilitated to their usual work and recreational treatment of Carcinoma of the Lung, W. F. Riehoff, *Ann. Surg.*, May, 1947, 125: 541.

—(W. H. Oatway, Jr.)

Cancer of Lung.—Cancer of the lung seems to be on the increase everywhere, and it is thirteen years since the first patient was successfully operated. This report deals with 280 cases, histologically verified, 51 per cent of which were operated. By sex, 220 were men and 60 women. The age varied from 18 to 77 years. Cough was the symptom which made the patient seek medical advice in 87 per cent. Fever was present in 54 per cent of those with secondary infection, pain in the chest in 49 per cent, hemoptysis in 43 per cent, dyspnea and wheezing in 30 per cent. No symptom or complex may be called truly typical. In 65 per cent the condition was masked by other possibilities, it having been diagnosed as tuberculosis (21.2 per cent), pneumonia (11.1 per cent), bronchitis (10.4 per cent), abscess of the lung (5 per cent), bronchial asthma (4.6 per cent), heart disease and pleurisy (3.6 per cent each), and so on. On an average, symptoms had been present for 3.7 months before seeing a physician, for six months before an X-ray was taken, and for 11.3 months before the diagnosis was made. X-ray changes are too variable to be conclusive. Bronchoscopy was performed in 251 cases and in 171 the accompanying biopsy settled the diagnosis. In the first five years of this study biopsies proved positive in 75 per cent, while in the second five years the figures have come down to 53 per cent. In other words, the earlier the biopsy, the more difficult it is to secure diseased tissue for examination. In 204 patients (75 per cent) the disease originated in one of the main bronchial tubes and in the rest in the smaller tubes. These latter cases are the ones in which bronchoscopy naturally fails. Conforming to the pattern in tuberculosis, the upper right lobe is the one most frequently affected (26 per cent), the upper left lobe coming next (18.3 per cent). Next to bronchoscopy, an exploratory thoracotomy (74 cases) or a biopsy of metastases (22 cases) proved to be the most reliable verification. Out of 275 cases diagnosed during life, 129 were found inoperable and 4 declined the operation. Radiotherapy is mentioned only to deplore the time it makes the patient lose in securing proper surgical treatment. In 7 cases the lesion was detected before symptoms developed, and in all but one this permitted removing the lung before metastases occurred.

in regional nodes. The operations included 73 exploratory thoracotomies, 27 palliative pneumonectomies, 40 curative pneumonectomies and 7 lobectomies. The operative mortality in the 74 excisions was 19.7 per cent for the whole period, but it decreased from 33.3 per cent in 1933-1936 to 9.8 per cent in 1940-1945. The lobectomies were made during the earlier period and proved too conservative. Living patients without metastases total 25 (7.5 per cent of 280 patients, and 52.5 per cent of 47 excisions). Five-year cures represent 1.5 per cent of the total series and 10.5 per cent of the 47 radically operated. (This study was made at the New England Deaconess Hospital in Boston.)—*Carcinome broncogénico: Estudio clínico y resultado del tratamiento quirúrgico en 280 casos*, L. Langer, *Prensa med. argent.*, May 23, 1947, 34: 932.—(A. A. Moll)

Induction of Bronchogenic Carcinoma in Mice.—Bronchogenic carcinomata were induced in mice from subcutaneous grafts of adult lung tissue impregnated with 2: methylcholanthrene. In mice of strain C3H, the tumor incidence was increased if the lung grafts were impregnated with stilbesterol in addition to the carcinogen. Histologically, the tumors were bronchogenic.—*Induction of Bronchogenic Carcinomas in Mice*, E. S. Horning, *Lancet*, August 9, 1947, 2: 207.—(A. G. Cohen)

Bronchogenic Carcinoma.—Thirty-six autopsied cases of bronchogenic carcinoma, observed between 1937 and 1945, were studied. These comprised approximately 8.6 per cent of all autopsies performed during this period at the Brooklyn Cancer Institute. Thirty-two, 88 per cent, were males. The mean age was 55.1 years; this is significantly lower than the mean age of many common malignancies. Nonproductive cough is the earliest and most common symptom. Bronchoscopic diagnosis is possible in the early stage when physical examination and X-ray examination are often negative. The development of asthmatic breathing in middle-aged individuals should arouse suspicion of a pulmonary carcinoma.

Secondary infection behind the tumor is frequent. When a portion of the obstructing tumor breaks down, the infection may subside temporarily. Atelectasis is frequent and is almost always associated with infection. Fever is often present and may lead to an erroneous diagnosis of pneumonia. Metastatic deposits are not infrequently the first clinical manifestation of bronchogenic malignancy; this is particularly important in cerebral metastases which may be mistaken for primary brain tumors. Cerebral metastases were found in 7 cases. Metastases occurred most frequently to the thoracic lymph nodes, the other lung, the liver, bones, adrenals and kidneys. The bones most commonly involved were the vertebrae, pelvis and femora. The mean and median life expectancies were eight months from onset of symptoms. All were dead within twenty-eight months. Interval X-ray study of a suspicious lesion is not justified. Roentgen therapy is indicated for palliation. Response to X-ray therapy cannot be predicted on the basis of cellular type. The carcinocidal dose is probably above 5,000 roentgens. There was no relation between administered tumor dose and longevity.—*Bronchogenic Carcinoma: A Clinical Pathological Study of 56 Autopsied Cases Seen at the Brooklyn Cancer Institute between 1937 and 1945 inclusive*, W. H. Henkin, *Ann. Int. Med.*, August, 1947, 27: 243.—(H. R. Nayer)

Intrabronchial Cancer Metastasis.—In a series of 1,200 cases of primary and secondary pulmonary cancer, 8 cases of intrabronchial metastases were found. Histologically, they were adenocarcinomata and assumed to be metastatic in origin. There was no true bronchogenic spread.—*Untersuchungen über Krebsmetastasen*, H. Walther, *Schweiz. Ztschr. f. Tuberk.*, 1947, 4: 319.—(B. Gerstl)

Surgical Resection for Metastatic Neoplasm.—The appearance of a solitary metastatic lesion in a lung months or years after the removal of a primary extrapulmonary sarcoma or carcinoma is not rare. Previously, there were 5 reported cases in which pulmonary re-

section had been done for this type of lesion; to these, the authors now add 19 of their own. Of the 24 cases, there was one operative death and recurrences in 11. Of the other 12, 8 are well twelve years to one year postoperatively; 4 were operated upon only recently. Six of 8 sarcomata and 6 of 15 carcinomata are apparently well. The operation was either lobectomy or pneumonectomy.—*Pulmonary Resection for Solitary Metastatic Sarcomas and Carcinomas*, J. Alexander & C. Haight, *Surg., Gynec. & Obst.*, August, 1947, 85: 129.—(A. G. Cohen)

Chest Injuries.—Injuries of the chest are responsible for about 25 per cent of battlefield deaths. In these cases roentgenoscopy is of value in the study of foreign bodies, fluid levels and lung reexpansion, in observing diaphragmatic mobility and thoracic cage motion, in detecting pleural fluid and adhesions, in studying heart configuration and motion. Traumatic conditions described include: pulmonary contusion and hematoma, simple, loculated and clotted hemothoraces, atelectasis, blast injury, bronchopleural fistula, missile tracks, and subcutaneous emphysema.—*Roentgenological Aspects of Battle Injuries of the Chest*, Major M. Rakofsky & Capt. V. P. Satinsky, *Am. J. Roentgenol.*, May, 1947, 57: 583.—(J. E. Farber)

Tropical Eosinophilia.—This syndrome was first described by Frimodt-Møller and Barton (1940) in southern India. Weingarten (1943) discovered that a short course of neoarsphenamine produced dramatic improvement. While tropical eosinophilia is not a rare disease in India and Ceylon, its existence in Africa has not as yet been generally recognized. The present study was carried out in Dar-es-Salaam, Tanganyika. Differential white counts were performed on a consecutive series of 34 male patients with symptoms of recurrent bronchitis or asthma. Eosinophilia of less than 20 per cent was found in 28 cases. In the 6 cases remaining, eosinophilia of 40 to 80 per cent was present. An additional seventh

case was referred because of an unexplained eosinophilia. Six were treated successfully with arsenic, while the condition regressed spontaneously in the seventh. Clinical findings were recurrent attacks of cough, wheezing, low fever, with asymptomatic intervals except for episodes of spasmodic coughing in the early morning. After a variable number of attacks, the interval of freedom became shorter, and cough and dyspnea caused increasing distress. Patients with long-standing illness complained of lassitude, anorexia and loss of weight. Three cases had no abnormal X-ray findings, while 3 had a mottled X-ray appearance. Red counts varied between 4,650,000 and 5,150,000, with hemoglobin from 94 per cent to 110 per cent, comparatively high for a country where anemia is prevalent. Leucocytosis varied from 11,250 to 34,000, with an eosinophilia of 52 to 78 per cent. The eosinophils often contained vacuoles. These disappeared in the course of treatment. Sputum for tubercle bacilli was negative. Four mites of *Tyroglyphus* and a few ova were found in specimens from case II, one mite of *Tyroglyphus* in case VI, and an unidentified mite in sputum from case IV. No mites were found in sputum from cases III and V. Löffler described a syndrome characterized by fever, cough and eosinophilia, with positive X-ray findings and rapid spontaneous recovery. It is unlikely that this is similar to tropical eosinophilia, which has had a known duration of as long as three years. Some think that tropical eosinophilia is an atypical form of asthma. However, the presence of fever, leucocytosis, splenomegaly and characteristic shadows in the X-ray of the chest would seem to differentiate it from Löffler's syndrome. Because of its close resemblance to infectious mononucleosis, the theory that it is a specific infection is favored, and, because of the presence of mites in the sputum, it is assumed that they are a direct or indirect cause of the disease. A similar condition has been reproduced in monkeys by the introduction of ova into the trachea. Treatment with inorganic arsenic is dramatically successful. The most effective method appears to be a ten-day course of carbarsone, followed

after a few days by four weekly injections of nearsphenamine (0.6 to 0.75 g.).—*Tropical Eosinophilia in East Africa*, H. T. H. Wilson, *Brit. M. J.*, June 7, 1947, 4509: 801.—(R. W. Clarke)

Benign Recurrent Meningitis.—The question raised in 1943 by the writer when reporting the first case of a peculiar mild recurrent lymphocytic meningitis is restated. Is it a new condition? The distinguishing and most interesting feature is its recurrent character and prompt subsidence. Mollaret reported (1944) 4 cases seen since 1928. Onset is sudden, usually in the afternoon, with fever, aching pains and meningeal signs, vasomotor disturbances and occasional vomiting and epileptic-like seizures. The attacks, which last twenty-four to forty-eight hours, continue for several years, at first every two or three months, and then once or twice every month. Finally, intervals between attacks lengthen until they cease completely. Spinal fluid is cloudy, opalescent and shows no pus, fibrin or tension, with preponderance of lymphocytes among cells present. Asthmatic episodes occurred between attacks. Discrete X-ray signs in the chest in 3 cases suggested a tuberculous allergy. Only the study of new cases can clarify the true nature and etiology of the condition.—*La meningitis multirrecurrente benigna, enfermedad nueva?*, J. Calvo Melendro, *Bol. Inst. de pat. méd.*, Madrid, March, 1947, 2: 45.—(A. A. Moll)

Portland Cement Dust.—The hypothesis that exposure to high concentrations of industrial dusts may lower resistance to acute pulmonary infections was investigated. In this paper, the effect of inhalation of cement dust on the resistance of rats to lobar pneumonia was studied. Portland cement contains less than one per cent of free silica. The animals were exposed for varying periods of time, two days to thirty weeks, to air containing the dust with an average of 200 million particles per cubic foot; 80 per cent of the particles were 3 micra or less in diameter. Intrabronchial inoculation with type one pneumococci was

then carried out. Control animals were used throughout and over one thousand rats were employed in the experiment. Resistance to lobar pneumonia was not lowered by exposure to the dust. Microscopic examination of the lungs of the exposed animals did not reveal any acute or chronic changes which could be ascribed to the dust. Petrographic studies indicated the progressive solution of the cement particles in the lungs without any resulting fibrosis.—*Effect of Portland Cement on the Lungs with Special Reference to Susceptibility to Lobar Pneumonia*, Anna M. Baetjer, *J. Indust. Hyg. & Toxicol.*, July, 1947, 29: 250.—(H. R. Nayer)

Bronchiectasis.—Nebulization therapy was used for 86 patients with chronic bronchiectasis. Forty-six patients were treated in preparation for excisional surgery, 40 patients were not suitable for surgical intervention. In all 86 patients penicillin aerosol was used, in 27 patients streptomycin hydrochloride was added to the penicillin solution for nebulization. In the latter group a combination of 200,000 units of penicillin with 0.5 to 1.0 g. of streptomycin dissolved in 20 to 30 cc. of isotonic sodium chloride solution was used for daily nebulization. In the majority of the surgical cases the volume of pulmonary secretions was reduced considerably in the preoperative period. The nonsurgical group was treated from two to eight weeks. The treatment was considered satisfactory if the daily volume of purulent secretions was reduced 75 per cent or more. Penicillin aerosol alone was effective in slightly more than half of the nonsurgical patients. Of 20 patients treated with combined penicillin and streptomycin aerosol 18 obtained a satisfactory result. Urticaria developed in 3 patients and arthralgia in 2 patients treated with penicillin aerosol. The reactions could be controlled by administration of benadryl. A valuable adjunct to nebulization therapy may be the direct intratracheal administration of penicillin and streptomycin.—*Nebulization Therapy in Bronchiectasis: The Use of Penicillin and Streptomycin*

Aerosols, A. M. Olson, J. A. M. A., July 12, 1947, 134: 947.—(H. Abeles)

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waltes & F. X. Byron, J. A. M. A., July 26, 1947, 134: 1069.—(H. Abeles)

Management of "Captive" Lung.—Decortication is used in military surgery to provide for expansion of a useful lung. This is accomplished by removing the "coat" or "peel" of organizing fibrin. This principle can be applied to civilian surgery. The requirements for pulmonary reëxpansion are: (1) some air must enter the lung, (2) the lung itself must be capable of reëxpansion and (3) the remaining content of the hemithorax must suffer a decrease in volume corresponding to requirement one. The factors concerned are: (1) bronchial obstruction, a) large bronchi, b) small bronchi; (2) pulmonary, a) defects of alveoli and interstitial tissue, c) defects of alveoli and pneumothorax, ii: bronchopleural fistula, valvular or non-valvular, b) fluid, c) fibrin, d) pleural investments. In evaluating a case, bronchoscopy and clinical study will elucidate factors one and two, while thoracocentesis will determine most features of factor three. In a case where there are no known bronchial and pulmonary factors, and where the lung will not reëxpand with pleural aspiration, a decortication must be done.—*Lung Mobilization: Its Indications in the Management of the "Captive" Lung*, H. T. Langston, *Surg., Gynec. & Obst.*, September, 1947, 85: 501.—(A. G. Cohen)

Arteriovenous Aneurysm.—A 27-year-old woman had cyanosis since birth, episodes of syncope and paroxysmal nocturnal dyspnea. Physical examination showed numerous, small, superficial hemangiomas on the face, lips and palms. The hemoglobin was 21.6 g., the red blood cell count was 8.2 million. The roentgenogram of the chest revealed a tumor in the right lower lobe. Following a lobectomy the cyanosis decreased, the hemoglobin dropped to 18.4 g. and the red blood cell count to 6.7 million. The pathological diagnosis was arteriovenous aneurysm measuring 4 cm. in diameter.—*Pulmonary Arteriovenous Aneurysm with Secondary Polycythemia: Report of the First Case Treated by Lobectomy*, W. H. Beier-

Aerosol Penicillin.—(1) A combined steam generator and aerosolizer is described, which effectively produces aerosols of penicillin whose inhalation is capable of providing good therapeutic levels of this agent in the blood. (2) Penicillin dissolves readily in propylene glycol to form an effective, stable aerosol. The addition of glycerin (5 per cent) further stabilizes the aerosol. (3) Methods of conserving the aerosol for maximum utilization include simple open inhalation; inhalation within an air-tight chamber or transparent portable tent, and inhalation from a breathing box. (4) Unusually high and prolonged levels of penicillin were obtained in the blood when a penicillin-propylene glycol aerosol was inhaled within a tent or from a breathing box. (5) The tent method should be ideal for the treatment of infants and children or whenever continuous treatment with penicillin is indicated. (6) Propylene glycol, by inhalation of its aerosol and by intravenous or intramuscular injection, imparts to the blood serum a pronounced inhibitory action against a strain of *Bacillus subtilis* (an attribute not possessed individually by either the propylene glycol or the serum). (Authors' Summary.)—*Aerosol Penicillin: Blood Levels of Penicillin by Inhalation of Aerosols Produced by a Combined Steam Generator and Aerosolizer, With the Use of Propylene Glycol, Tents and a Breathing Box*, S. J. Prigal, T. H. McGavack, F. D. Speer & R. Harris, J. A. M. A., July 12, 1947, 134: 932.—(H. Abeles)

Bronchial Catheterization in Lung Abscess.—The treatment of lung abscess with direct penicillin instillation into the abscess cavity is outlined. Among the cases under observation 40 per cent of abscesses were found in the dorsal segment of the upper lobe, 15 per cent in the middle lobe, and 13 per cent in the right lower lobe; 75 per cent of abscesses were localized in the right lung. The technique of introducing the catheter into the various pulmonary

segments is described in detail. The dosage of penicillin was 100,000 units in 10 cc. of saline instilled directly into the abscess cavity. In acute severe cases instillations were performed once daily for a period of ten to fifteen days. In milder cases a total number of 6 to 8 instillations were given every other day. If necessary the series was repeated after an interval of one week. The method is said to be without serious accidents. Hemorrhage, without any further consequences, occurred 5 times in 1,500 instillations. No statistical data on results are given.—*La localisation radiologique des cavités suppurées intrapulmonaires et leur cathétérisme par voie endobronchique*, C. Mattei, M. Tristani & A. Barbe, *Rev. de la tuberc.*, 1947, 2: 704.—(V. Leites)

Mediastinal Emphysema.—Block of the brachial plexus to produce anesthesia of an upper extremity has received increasing use in military surgery. The present series of 700 cases includes many plastic surgery operations, for which brachial block is quite suitable. To inject the plexus the needle is inserted above the middle of the clavicle and aimed downward towards the plexus and towards the apex of the lung. Pneumothorax has been reported as a complication, and even in association with emphysema of the lung and subcutaneous tissues. Five instances of mediastinal emphysema are reported for the first time in the present series. The signs and symptoms of mediastinal emphysema are emphasized by the report of a typical case, in which a pneumothorax developed during the twenty-four hours after the mediastinal changes were noted. None of the 5 patients had any serious respiratory difficulty or complication.—*Mediastinal Emphysema Secondary to Brachial Plexus Block*, E. G. Dimond, B. Root & M. H. Delp, *Bull. U. S. Army M. Dept.*, August, 1947, 7: 718.—(W. H. Oatway, Jr.)

Ossification of Bovine Lung.—The first known case of ossified lung in a domestic animal is reported. Ossification of bronchial cartilages and tuberculous or other pulmonary lesions are common in man, but diffuse forms

are rare; only 46 cases had been reported until 1943. There are two varieties of diffuse ossification, the racemose or branching type and the nodular circumscribed type. The racemose is by far the more common, and consists of branching spicules of true bone in the inter-alveolar septa of the lung. They may be the result of a senile metaplasia in the perivascular connective tissue. Marrow-formation is relatively rare in the diffuse forms. The present case report is that of a Texas steer, condemned in a sale-yard because of extreme emaciation. The nodes and other organs were normal, but the lungs were hard and inelastic, especially in the posterior areas. Typical bone-islands ("disseminated" ossification, similar to the racemose type), as well as exudative and proliferative changes, were found in the septa. Some alveoli were atelectatic, while others were emphysematous. Osteocytes were numerous in the bone, but osteoclasts and osteoblasts were absent.—*A Case of Ossification of the Bovine Lung*, W. S. Bailey, *J. Am. Vet. M. A.*, August, 1947, 111: 123.—(W. H. Oatway, Jr.)

Giant Mediastinal Teratoma.—This case raised the old, and often difficult problem of the correct diagnosis in a condition characterized only by an increasingly large X-ray shadow in the chest. Throughout the final eight-year course of the disease a number of possible diagnoses were advanced, including pneumonia, hydatid cyst, aneurysm, growth of the thymus, lymphosarcoma, intrathoracic goiter and, finally, because of the mediastinal location and tomographic findings, dermoid cyst. In order to verify this assumption, an exploratory puncture was performed, which yielded a typical brown fluid. A series of punctures furnished some relief but the increasing respiratory difficulty and general exhaustion required surgical treatment. An anterior mediastinotomy was well borne and proved successful in removing over 2,000 cc. of hair, sebaceous matter and cystic fluid. Present condition of the patient is excellent, with gain in weight, normal respiration and ability to sleep.—*Teratoma gigante de mediastino*, M.

Benzo, Bol. Inst. de pat. méd., Madrid, February, 1946, 1: 23.—(A. A. Moll)

First Case of Histoplasmosis in Colombia.—A case of histoplasmosis is described as a post-mortem finding. The patient was a woman 56 years old, a native of Venezuela, who died in the Cúcuta hospital after a seven-day illness. Typhoid was reported as the cause of death. This is the first case of the disease seen in Colombia and the diagnosis was confirmed both by Colombian and Brazilian experts. Histoplasmosis has been described from various parts of South America since Darling first found it in Panama in 1906. Negroni in Argentina reported the first South American case in 1940.—*Histoplasmosis en Colombia, A. Gast Galvis, Rev. de med. y cir., Colombia, S. A., May, 1947, 14: 12.*—(A. A. Moll)

Histoplasmosis.—Two cases have been recorded from Wisconsin to bring the total number of reported cases to 80. It is generally a fatal systemic disease caused by the yeast-like fungus named *Histoplasma capsulatum* which may be found in the reticulo-endothelial system and is probably transmitted from animals, notably dogs. The four principal clinical features of the disease are: (1) gastrointestinal manifestations of ulceration and diarrhea, (2) skin findings of chronic ulcerations and abscess formations, (3) cardiac or joint manifestations, (4) lymphadenopathy, hepatomegaly and splenomegaly. Lung findings are recorded in about 20 per cent of the cases and are not characteristic and frequently are confused with tuberculosis, especially the pulmonary calcifications. The cases of histoplasmosis have usually presented a gross picture similar to that of leukemia. Caseous necrosis of the adrenals is particularly common in these patients. Histologically the organisms are found throughout the reticulo-endothelial system contained in the phagocytic reticulum cells. Secondary anemia, leukopenia and thrombocytopenia have been frequent. It is of interest that the majority of histoplasmin reactors are demonstrated between 5 and 25 years of age; whereas, the tuberculin reactors are found in the third

and fourth decades. In those who are histoplasmin-negative and tuberculin-positive, the incidence of pulmonary calcifications is about 17 per cent; those with histoplasmin-positive and tuberculin-negative skin tests have pulmonary calcifications in slightly more than 90 per cent.—*Histoplasmosis: The Pathological and Clinical Findings, J. F. Kuzma, Dis. of Chest, July-August, 1947, 13: 338.*—(E. A. Rouff)

Osteochondritis Vertebræ (Calvé).—Descriptions of this condition are very misleading. The correct definition is *osteochondritis vertebræ* of the primary ossification centres occurring before age 10. It is thus distinguished from *osteochondritis vertebræ* of the secondary ossification centres (epiphyseal plates) often named Scheuermann's disease or juvenile kyphosis. The author speculates that Calvé's disease may be caused by tubercle bacilli of low virulence. A case is reported.—*The Relationship between Tuberculosis and Osteochondritis Vertebræ (Calvé), F. Leeser, Am. J. Roentgenol., June, 1947, 57: 744.*—(J. E. Farber)

Tuberculosis Control.—The problem of tuberculosis control in the French army may be considered under three main headings: (1) the discovery and elimination of all tuberculous personnel as soon as possible after induction, (2) maintenance of health of the standing army, and (3) prevention of spread of the disease in the civilian population by discharged tuberculous army personnel. In order to accomplish the first aim, those called to active military duty are required to bring health certificates from their own physicians. These certificates in conjunction with a preliminary examination by a medical board eliminate a certain number of persons who are then sent to a chest centre for clarification. All those passed upon by the first board are brought up before a review board. There they are subjected to an even more detailed examination including systematic radiography of the chest. All abnormal conditions are referred to a special chest centre where they

are classified into the following groups: open tuberculosis, closed tuberculosis, suspected tuberculosis, pleural or pleuropertoneal tuberculosis, and "surgical" tuberculosis (including lymph node, genitourinary, bone and joint, etc.). To achieve the second aim, namely the maintenance of health of the existing army, military physicians are constantly primed on recognition of early signs and symptoms. A continuous fight against predisposing causes, such as they are known, is waged by the army medical personnel. The most effective weapon in this fight is the periodic X-ray reëxamination of all personnel. The number of cases discovered by such means is still considerable, amounting to 0.8 to 0.9 per thousand in a group so examined. In 1946, tuberculin testing of recruits was done, and it was found that nearly 50 per cent were tuberculin-negative. Retesting of the nonreactors will be done in the future as a case-finding measure. Universal vaccination of these troupes with BCG is not being planned in spite of the favorable report of the Academy of Medicine. Vaccination will be limited to volunteers. Further measures consist of careful examination of all contacts of recently discovered cases, and case-finding among the patients' families. Diagnosed cases are placed under medical care as soon as possible. Patients may be institutionalized either in civilian institutions by arrangement, or in one of several government hospitals. Facilities are also available for institutional or preventorium care of dependents of personnel, should such become necessary. In order to safeguard the health of the civilian population, part three of the army's program, a very comprehensive medical-social program is available. The individual and family problems of each patient are worked out by the social agencies in such a manner that the patient is satisfied to accept treatment until he can be discharged safely. Considerable benefits are offered in this connection. The comprehensive program as here outlined is in force for almost one million personnel, both male and female. In addition to all enlisted and commissioned

personnel it comprises the women's army corps, children and adolescents in military preparatory schools, officer candidates, all dependents of regular army personnel, and all civilian workers employed by the war department.—*La prophylaxie de la tuberculose dans l'Armée française*, Debenedetti & Dutrey, *Schweiz. med. Wchnschr.*, May 31, 1947, 77: 591.—(H. Marcus)

Hospitalization Cost.—Data on the cost of methods for control of tuberculosis in general hospitals have not been available. The need, feasibility and value of control methods are now well known—personnel members should be recurrently examined by a suitable X-ray method; all newly registered patients and outpatients should be screened by radiography for tuberculous disease; and tuberculous patients, whether admitted for therapy or newly-found, should be cared for with adequate isolation technique. Unrecognized disease among new admissions, and the hazard to personnel in contact with patients have been demonstrated. Control procedures are increasing but not wide-spread enough. Accounting methods, disinterest, and a fear of the results have further limited the field from which data can be obtained. For the present survey, information was obtained from hospitals and sanatoria which were known to have experience with control measures; they are of various sizes and types, and are in four different areas of the United States. Cost data were also obtained from the health departments of five states, from several hospital, radiology, and tuberculosis societies, and from the U. S. Public Health Service. All of the data are previously unpublished. The general costs of tuberculosis to society, the state, and to individuals are mentioned. The cost of care of tuberculous patients in sanatoria is presented as a comparison to the cost in general hospitals. The cost and charges for care of tuberculous and nontuberculous patients in hospitals were obtained from twenty administrators of general hospitals. The hospitals included several with a 95- to 200-bed capacity, and several with 500 to

3,400 beds. The figures differ widely, depending on the type of hospital, the services rendered, and the size of the unit. They were mostly derived from experience during the fall and winter of 1946-1947. Analysis of the data shows the surprising fact that *cost and charges for care on tuberculosis units were usually the same or less than for care on other services*. In large tuberculosis units the cost was markedly less, and comparable to sanatoria of a similar type. The same services were provided, plus some degree of infectious disease precautions and, frequently, chest surgery. A survey of the expense of isolation technique was made and listed. Many hospitals and sanatoria use only a few essential sanitary procedures. The total cost of precautionary methods could not be estimated, but basic services cost little if any more than for care of nontuberculous patients, and basic materials cost only a few cents a day per patient. (Whatever the cost, it is already included in the low cost of care.) The cost of constructing facilities for care of tuberculous patients is discussed. New construction is expensive and rarely necessary; the usual need is for small units or rooms, and these may be had by conversion of existing space at a very low cost. The costs of compensation and insurance are discussed—the former is high and rising; the latter has not yet been affected by use of control measures, although the door is open whenever sufficient experience shows a favorable result. The use of subsidies to cover the costs of control measures has been investigated. Many hospitals are now given partial or complete support for case-finding surveys from various sources. Many states now subsidize the care of some (or most) tuberculous patients in order to obtain cooperation, isolation and care. The federal government, through the Veterans Administration and hospital-aids program, has shown the same tendency. The cost of case-finding by X-ray methods is described. A relatively small number of hospitals has a complete survey program, though it is increasing quite rapidly; the most suitable method will depend upon the money or equipment available, and on the case-load. Small hospitals will probably use full-size films on paper X-rays; the cost per patient should range between 50 cents and a dollar, plus possible reading costs. Large hospitals, and those able to afford special equipment, will use miniature films of some sort. None of the hospitals which use small films had data on costs, due to the use of subsidies, but figures were obtained from numerous surveys by the U. S. Public Health Service. Such figures had to be included, and have increased since 1943-1945. The range was from 21 to 69 cents per capita, which can be reduced 30 to 75 per cent in stationary hospital units by the subtraction of travel costs, salaries, publicity, etc., and by the use of existing hospital equipment and personnel. The cost of film-reading is minimized by the help of staff members and the cooperative attitude of the College of Radiologists. The cost of new photoroentgen equipment ranges from \$3,800 to \$5,500 for machines without energizing equipment, to \$9,000 or more for complete units. Most hospitals have absorbed the cost of case-finding, but a few are known to charge a flat-rate fee, the same as for admission blood tests.—*The Economics of Tuberculosis in General Hospitals*, W. H. Oatway, Jr., *Hospitals*, November, 1947, No. 11, 21: 54.—(W. H. Oatway, Jr.)

Primary Tuberculosis.—A group of children from tuberculous families giving evidence of latent or manifest primary infection was subjected to periodic follow-ups between the years 1925-1941. The initial group consisted of 378 children up to the age of 4. In this group 236 cases showed only a positive tuberculin reaction, 120 had pulmonary foci and adenopathies and 22 had acute progressive forms (miliary tuberculosis, caseous pneumonia). The total tuberculosis fatality in this age-group was 9.5 per cent (34 cases), two-thirds of which fell into the first year. The next group included 270 children between the ages of 5 and 10 with a tuberculosis

fatality of 3.7 per cent, almost exclusively from tuberculous meningitis. The incidence of pulmonary foci was lower than in the first group. There were 4 cases of benign pulmonary infiltrations and 8 cases of extrapulmonary tuberculosis. In 1940-1941 a group of 218 children between the ages of 11 and 18 underwent the final examination. Among the 118 cases in the age-group 11 to 13, 6 cases had benign lung involvement in form of circumscribed infiltrations or disseminated lesions. One-third of the whole group gave evidence of what is described as chronic "tuberculous intoxication" which is being attributed to persistent activity in the lymph node component of the primary complex. In the age-group 14 to 18 only 64 per cent could be considered as in good health. The others gave evidence of active primary tuberculosis in its protracted form with different clinical manifestations or various forms of pulmonary tuberculosis mostly localized in the upper lung-fields with tendency to progression. Among 52 adolescents in the age group 16 to 18, every fifth showed a relatively fresh pulmonary process, every tenth had a positive sputum. The connection of these grave progressive forms with primary infection acquired in early childhood is considered most probable. In another group of 94 children having been exposed to tuberculosis in childhood, 13.2 per cent developed tuberculosis during adolescence, whereas among 124 children from nontuberculous milieu the incidence of pulmonary tuberculosis during adolescence was only 7.2 per cent. The effect of continued superinfection on latent or active primary tuberculosis could not be definitely established on this material: a group of 38 children infected during early childhood and subjected to prolonged or repeated superinfection until adolescence developed pulmonary tuberculosis in 10.5 per cent of cases. The incidence of pulmonary tuberculosis in a similar group with no possibility of superinfection was 9.5 per cent.—*Early and Remote Effects of Tuberculous Infection Acquired during Early Childhood,*

B. L. Jacknis, Probl. tuberk., 1947, No. 3, 26.—(V. Leites)

Primary and Reinfection Tuberculosis.—Tuberculin studies both in animals and persons have demonstrated that the body may lose, after a certain period, its ability to react to tuberculin. The finding in adults of modalities affecting both nodes and lungs, and comparable in every way to those seen in primary infection in children, led to the belief that they represented late primary infections. The detection of this type of lesion in patients tuberculized long before and having signs or history of an old tuberculous process shows that cascated nodes should be attributed to constitutional peculiarities unconnected with tuberculin allergy. At present, it is impossible to establish the diagnosis of primary infection in adults, as it cannot be based on the reversion of the test or the verification of an infantile type tuberculosis. Differentiation of primary and reinfection lesions is difficult and, as shown by Israel and Long, has no practical value. On the other hand, recognition of the node involvement becomes significant because the course is frequently more serious in this type. The new genetic studies, supplementing biometric and general data, have demonstrated the hereditary transmission of a greater degree of resistance or susceptibility to tuberculosis in receptive animals and persons. When considering the clinical, epidemiological and social aspects of the disease, the significance of the soil factor cannot be disregarded. The observations made among the Bolivian Indians during the Chaco War and by Marais (1946) among South African natives working in the mines bear out this conception, which has also been emphasized by Monge in Peru. Pathological and X-ray studies by Scandroglio and Rodríguez among people of all ages dying from violent causes in Montevideo showed that at about 22 years of age calcifications are found in 100 per cent of cases, while tuberculin reactor rates at that age do not exceed 80 per cent. In other words, 20 per cent of those people (and the percentage is

even higher at the age of 15) have lost their ability to react to tuberculin.—*La tuberculosis primaria y de reinfección del adulto (su significado clínico, epidemiológico y social)*, F. D. Gómez, *Clin. tisiol (Rio de Janeiro)*, October-December, 1946, 1: 285; and also *Rev. brasil. de tuberc.*, November-December, 1946, 15: 489.—(A. A. Moll)

Perforating Lymph Nodes.—In the opinion of Mounier-Kuhn and Dufourt perforation of caseous lymph nodes into the bronchus following active primary tuberculosis is a much more frequent occurrence than hitherto suspected. The authors are here not referring to the well known manifestations of perforation in its massive form, but to its less pronounced aspects. Routine use of bronchoscopy in adults and children with primary infection revealed the frequent presence of very small bronchial fistulae, often difficult to visualize because of secretions or edema of the bronchial wall. These bronchoscopic findings were seen in association with a very characteristic X-ray pattern: there was a more or less circumscribed area of fine, nodular, partly confluent infiltrations extending from the hilum and usually not quite reaching the periphery. Tomography revealed in the region of the infiltration the image of a bronchus with thickened contours, indicating disease of the bronchial wall. Clinically these small perforations remained mostly silent or gave few uncharacteristic symptoms. The prognosis was good. There was spontaneous closure of the bronchial fistulae. The pulmonary infiltrations persisted for three to six months and then showed gradual regression. If the perforation was larger the pulmonary involvement due to bronchial dissemination was more extensive occupying a pulmonary segment or a whole lobe. These cases, without being alarming or rapidly fatal, have a more serious prognosis and pneumothorax should be considered. Fibrotic or calcific changes formed a residue of these pulmonary infiltrations. The X-ray film of a child or adolescent showing a circumscribed area of multiple small calcific

densities, situated mostly in the middle or lower lung-fields, permits according to the authors to make a retrospective diagnosis of curable lymph node perforation into the bronchus during the course of primary tuberculosis. It is stressed that the described pulmonary infiltrations, belonging to the primary and post-primary period, should be strictly differentiated regarding pathogenesis, prognosis and treatment from infiltrations of the reinfection period, such as the early infiltrate or others, which they may resemble roentgenologically.—*Les infiltrats pulmonaires secondaires d'origine ganglionnaire*, A. Dufourt & P. Mounier-Kuhn, *Rev. de la tuberc.*, 1947, 11: 155.—(V. Leites)

Tracheobronchial Tuberculosis.—Among 151 patients (73 men and 78 women) in a tuberculosis hospital in Rio de Janeiro bronchoscopic examination revealed in 59 (39 per cent) tracheobronchial lesions. In 40 some type of collapse therapy was tried: 24 pneumothoraces, 12 thoracoplasties, 3 phrenicectomies (with very poor results), and one extrapleural pneumothorax. In a two-year period 7 of these 40 cases (11.8 per cent, as compared to 21.2 per cent in the entire group) died, 13 progressed unfavorably, 5 became arrested and 14 either improved considerably or healed clinically. When tracheobronchial and visceral pleural lesions coexist pleural complications may develop during pneumothorax treatment. Although pleural lesions seem more responsible, there should not be disregarded the possibility that empyema may be due to the spread of the suppurative process caused by the catarrhal retention. All changes in the mucous membranes in the trachea and larger bronchial tubes, including extensive catarrhal infiltration, were listed, tuberculous and secondary bacterial processes being usually associated. In local treatment, even when tuberculous ulceration was present, sulfanomides or penicillin was tried. Pleuroscopic examination should decide whether pneumothorax should be continued in such cases or another method of treatment substituted.—*A traqueo-*

broncoscopia na tuberculose pulmonar, Clin. tisiol. (Rio de Janeiro), January-March, 1947, 2: 29.—(A. A. Moll) (The Third Brazilian Tuberculosis Congress adopted a resolution recommending surveys in tuberculosis services to determine the prevalence of tuberculous tracheobronchitis and the Seventh Pan American Tuberculosis Congress also adopted a resolution on this subject. A. A. M.)

Trauma and Tuberculosis.—If trauma is to be indicted as causing or aggravating tuberculosis the time element must be such as to exclude all possible doubt of a casual connection. Such was judged to be the case in 2 patients reported by the author. A man of 53 who had always been in good health tripped and hit the right lower lateral chest severely. Eight days later hemoptysis occurred, and within thirty-six days the patient had the well marked clinical picture of miliary tuberculosis to which he succumbed in another month. Chest X-ray films taken shortly after the injury showed only the presence of a calcified primary focus in the right lower lobe. In due time the characteristic X-ray picture of generalized miliary tuberculosis was observed. Autopsy showed a partially calcified chalky focus in the right lower lobe with a lymph node component, also calcified, in the lung root. There was fresh miliary seeding, and also localized aspiration tuberculous pneumonia due to the recent hemoptysis. The pleura over the primary focus was adherent, and there were hemosiderin deposits in the pleural scar. This latter fact proves beyond doubt that the original trauma occurred precisely in the area of the primary focus and was responsible for the developments. The second case is that of a female patient who had been treated for active tuberculosis in the past, but whose condition was inactive at the time of the injury. Blunt trauma to the lower abdomen was followed within twenty-four hours by temperature elevation which persisted. In the course of time, first symptoms and then signs of reactivation occurred, the sputum becoming positive later on, and this was followed by

development of a new lesion. This patient had a paralyzed right diaphragm, and the base of the right lung was adherent to it. It is felt that the full force of the blow was transmitted to the right lung because of the phrenic paralysis, thus causing great stretching and tearing of the original lesions. It was eleven months before the *status quo ante* was reached.—*Über traumatische Tuberkulose, W. Löffler, Schweiz. med. Wchnschr., June 14, 1947, 77: 687.*—(H. Marcus)

Diabetes and Tuberculosis.—The association of diabetes and tuberculosis becomes more common as diabetic patients are more carefully scrutinized. In a series of over 100 cases seen in the Buenos Aires Tuberculosis Research Centre all types of diabetes were seen. Women prevail, but this is because the centre has the only service in the city for this type of female patients. Foreign statistics are far apart as to the proportion of tuberculosis among diabetic patients. Rahtery-Marie and Ray in France found 16.5 per cent among their clientele. Wilder and Adams in the United States reported only 1 per cent among 1,000 diabetes cases. Von Noorden in Frankfort gave 5.5 per cent for his private practice and 15 per cent for his hospital cases. In opposition to Root's report for the United States, in Argentina tuberculin tests have proved equally positive in diabetic as in other children. The proportion of those in whom the two diseases begin simultaneously or quite closely does not exceed 5 per cent in the Argentine series. Death rates were very high in the Argentine group because of the patients' advanced age and their poor condition. All deaths were from tuberculosis. In 6 cases with a fulminating hemoptysis atheromatous lesions of the pulmonary artery were found at necropsy. About 75 per cent of the patients needed insulin. In no case were the alleged pulmonary reactions to the drug observed. For the treatment of tuberculosis in these patients the usual measures are indicated with the necessary precautions.—*Diabetes y tuberculosis, R. A. Izzo, Rev. brasil. de tuberc.,*

Emphysema in Tuberculosis.—Emphysematous changes in pulmonary tuberculosis may be classified as intrafocal, perifocal, interstitial, diffuse (compensatory), bullae and blebs. The pathogenesis of intrafocal and perifocal emphysema is bronchial and bronchiolar obstruction. The perifocal form is the most common type. Interstitial emphysema is found in artificial and spontaneous pneumothorax. A bleb is formed when the lung is separated from the pleura by interstitial emphysema. In bullae the pleura retains its connection with lung parenchyma. Primary tuberculous foci may be enveloped in microscopic areas of perifocal emphysema. Hematogenous tuberculous foci may show several types of emphysema: intrafocal, bullae and blebs. The chief cause of localized hypertrophic emphysema is bronchial obstruction. The latter is produced by exudate, necrotic material, endobronchial tuberculous lesions, compression, torsion and stretching. Atrophic emphysema is largely due to vascular changes.—*Pulmonary Emphysema and Tuberculosis*, A. Guggenheim, *Am. J. Roentgenol.*, July, 1947, 58: 64.—(J. E. Farber)

Tuberculostasis by Streptomycin.—The present study was undertaken for the purpose of clarifying the bacteriostatic vs. the bactericidal effects of streptomycin on *M. phlei*; *M. avium*; *M. tuberculosis* var. *hominis* no. 607, nonpathogenic strain; *M. tuberculosis* var. *hominis* H37Rv, pathogenic strain; *M. tuberculosis* var. *hominis* H37RvR, streptomycin-resistant pathogenic strain. The method of growing the organisms for bacteriostatic tests has been described elsewhere (Smith, 1947). For bactericidal studies, the cultures were plated out on suitable agar media, incubated for varying periods of time at 37°C., and all colonies counted. The results show that streptomycin has not only a bacteriostatic but also a marked bactericidal action upon different strains of *M. tuberculosis*. The size of the inoculum and the time of incubation

are of great importance in determining the bacteriostatic and bactericidal activity of the antibiotic. In a growing culture of tubercle bacilli, there was a decrease rather than an increase in the proportion of streptomycin-resistant cells with an increase in age of the culture. When streptomycin and streptothricin were combined, their effect upon tubercle bacilli was additive rather than synergistic. The principal effects of streptomycin on the morphology of tubercle bacilli were loss of acid-fastness, increase in granulation, and, in highly bacteriostatic concentrations, shortening of the rods.—*Tuberculostatic and Tuberculocidal Properties of Streptomycin*, D. G. Smith & S. A. Waksman, *J. Bact.*, August, 1947, 54: 253.—(F. G. Petrik)

Streptomycin Resistance.—To study some of the factors which result in the production of streptomycin-resistant strains of tubercle bacilli, sputa of 8 patients having far advanced pulmonary tuberculosis and being treated with the drug were used in experimental work. Cultures were obtained before institution of treatment and at weekly intervals thereafter for a period of four to five months. All cultures were made on Herrold's glycerine-egg medium. Sensitivity of the bacilli to streptomycin was determined at the first inoculation by adding streptomycin in varying concentrations to the medium and inoculating plates of plain and streptomycin-containing media simultaneously with equal amounts of treated, concentrated specimen of sputum. To determine the potency of streptomycin after it had been added to Herrold's medium, assays were carried out over a period of seven weeks, using a modification of the cup method of Stebbins and Robinson. No appreciable diminution of potency of streptomycin was detected. Paper day intramuscularly, in divided doses at six-hour intervals. In 7 of the 8 cases a few relatively resistant organisms were found to be present in cultures before institution of chemotherapy. In 4 of the cases, the original

predominantly sensitive strains of bacilli isolated were replaced during chemotherapy by strains more resistant to the drug. Weekly cultures showed a gradual increase of the number of resistant organisms, beginning one to four weeks after institution of therapy. It was observed that resistant organisms grow comparatively slowly on media containing streptomycin, although the rate of growth tends to increase as greater degrees of resistance appear. Although the mechanism of drug resistance is an unsolved problem, evidence indicates that the factors of genetic variation and selection may be of prime importance.—*Relative Numbers of Resistant Tubercle Bacilli in Sputa of Patients before and during Treatment with Streptomycin*, Marjorie Pylé, *Proc. Staff Mecl., Mayo Clin., October 15, 1947, 22: 465.*—(P. Q. Edwards)

Streptomycin for Miliary Tuberculosis.—An infant of 11 months was found to have miliary tuberculosis in September, 1946. Biopsy of a cervical lymph node was positive. One gram of streptomycin per day was given for three months, and was then discontinued because of severe local reactions to the injections. Fever disappeared twenty-four hours after the drug was exhibited; lung signs began to clear in a few days; the lymph nodes were almost normal at five weeks; the miliary lesions in the lungs had cleared by the seventh week of treatment. Normal findings were present at an examination a month after cessation of therapy.—*Streptomycin in the Treatment of Miliary Tuberculosis*, G. Cobley & E. Goettsch, *J. Pediat., July, 1947, 31: 70.*—(W. H. Oatway, Jr.)

Streptomycin for Tuberculous Sinuses.—Eleven Negro patients and one white patient with 60 draining, proven tuberculous, cutaneous sinuses were treated with streptomycin. They received 0.3 g. every four hours, 6 patients for a period of ninety days and 6 patients for a period of 150 days with an interruption of three weeks after the first ninety days. In 9 patients the sinuses developed

from bone lesions, in one following laparotomy and in one it originated in the ischiorectal area. The average length of time the sinuses existed prior to the institution of streptomycin therapy was twenty-four months. Nine sinuses closed within one to four weeks, 9 within six to eight weeks, 30 within ten to twelve weeks and 11 within thirteen to twenty weeks. One sinus is still draining but has shown definite improvement. When a large cold abscess exists in conjunction with tuberculosis of the vertebrae, there is little tendency for the pus to disappear under streptomycin therapy unless it is evacuated by open drainage. Necrotic bone or cartilage should be removed. The average period of observation following closure of the sinuses is four months.—*Streptomycin in the Treatment of Draining Tuberculous Sinuses*, B. L. Brock, *J. A. M. A., September 20, 1947, 135: 147.*—(H. Abcles)

Para-aminosalicylic Acid.—The efficacy of para-aminosalicylic acid in experimental tuberculosis is being investigated by numerous workers at the present time. A recent study of use of the drug in guinea pig infection has yielded pertinent information. Each of a series of adult male guinea pigs was inoculated subcutaneously with 0.001 mg. of human type bacilli, strain H37Rv. Six weeks later all the inoculated animals were noted to be sensitized to tuberculin administered subcutaneously. Starting on the forty-second day after infection, 17 of the animals were treated daily with para-aminosalicylic acid (PAS) by adding 4 per cent by weight of the drug to the feed, about 1.6 g., and 20 animals served as untreated controls. After 161 days of observation (119 days of medication) the surviving animals were killed for necropsy. Severity of disease recorded for each of the untreated controls leaves no doubt of the potential virulence of the infecting organism. In the treated group, the amount of disease varied inversely with the period of treatment—almost no infection was found in the 9 animals treated for the full 119 days. Concentration of the drug was found to be less

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than 0.5 mg. per 100 cc. of blood at the time of autopsy. No toxic effects of PAS were observed. Potential effectiveness of PAS in tuberculous infection is indicated by these results, in view of the fact that the disease had been established six weeks prior to the beginning of treatment and in those animals that received the drug for the maximum period of treatment the deterrent effects on the disease were definitely impressive.—*Para-aminosalicylic Acid in Experimental Tuberculosis in Guinea Pigs*, W. H. Feldman, A. G. Karlson & H. C. Hinshaw, *Proc. Staff Meet., Mayo Clin., October 17, 1947*, 22: 473.—(P. Q. Edwards)

drug was started simultaneously with the inoculation of the animal. After prolonged treatment degenerative changes were noted in the liver and the kidneys.—*Chemotherapeutic Activity of Some Sulphones in Experimental Tuberculosis*, U. K. Weisfeiler, *Probl. tuberk., 1946*, No. 4, 51.—(V. Leites)

Subtilin.—The present communication deals with the use of a slightly modified Dubos and Davis medium to demonstrate the antibiotic activity of subtilin against a virulent strain of *M. tuberculosis*. The results show that although subtilin regularly inhibited the growth of the strain of mycobacterium used in concentration of 1:400,000, subsequent animal inoculation revealed that its bactericidal property *in vitro* was low. It required a concentration of 1:20,000 to sterilize the organisms employed in these tests. Unpublished data indicate that subtilin is precipitated in the presence of sodium chloride. Concentrations of subtilin (University of California Lots 8 and 10) greater than 0.1 mg. per cent appear to be precipitated in the blood. Nevertheless, the marked bacteriostatic effect shown here in conjunction with the low toxicity of subtilin are favorable indications for therapeutic trials. A less toxic salt-soluble fraction of subtilin is now available for such trials.—*Use of Modified Dubos Medium for Demonstration of Antibiotic Activity of Subtilin against Mycobacterium tuberculosis*, S. C. Wong, A. S. Hambly, Jr. & H. H. Anderson, *J. Lab. & Clin. Med.*, July, 1947, 32: 887.—(F. G. Patrik)

Promin and Diasone.—The effects of promin and diasone as prepared by the Academy of Medical Science of the U. S. S. R. according to the instructions of Feldman were studied *in vivo* and compared to the effects of the imported American products. The experimental animal for promin was the white mouse. It appeared that the Soviet product was of much lesser toxicity than the American one and could be given in daily doses of 30 to 40 mg., whereas the maximum tolerated dose of the American promin was only 15 mg. daily. With this dosage the American promin was found to be ineffective in inhibiting experimental tuberculosis. Soviet promin was given in the above dosage for twenty days to white mice which had been infected intravenously with a virulent culture of bovine bacilli. A definite inhibitory effect on the development of tuberculous infection was noted in these animals as compared to controls. In analogy to the American experiments, diasone was studied on guinea pigs. The daily oral dose was 300 mg. The duration of treatment was seventy-eight to ninety-six days. The animals had been inoculated with a mixture of equal parts of virulent human and bovine type bacilli. The results of these experiments seem to indicate a high chemotherapeutic activity of diasone towards tubercle bacilli, of the human as well as of the bovine type. The maximum therapeutic effect was achieved if administration of the

Subtilin in Tuberculosis.—First human experiments with subtilin, conducted in 1944, failed to show any therapeutic merit in the drug discovered by Fontes Magarão. This was probably due to impurities in the product, as previous results *in vitro* and in animals had been encouraging. A new purified extract was made available by Fontes Magarão in 1946 and used in the present clinical study. Eight cases of pulmonary tuberculosis of various types are reported in all of which general improvement, although in varying

degree, followed the use of subtilin. The new preparation may be used orally or intramuscularly and was employed in both ways in this series. The usual oral dosage is 20 drops a day, taken on an empty stomach. No adverse reactions have been noted so far. Subtilin may be tried either alone or to supplement the accepted methods of treatment. Salle and Jane in Los Angeles are also conducting a trial of the drug.—*Nota previa sobre a ação terapêutica da subtilina na tuberculose pulmonar*, A. Renzo, *Rev. méd. munic.*, (Rio de Janeiro), October-December, 1946, 9: 96.—(A. A. Moll)

Surgery for Pulmonary Tuberculosis.—Argentine statistics support those abroad showing that among tuberculosis patients operated, in one-third the disease heals, in one-third it is not influenced and in the remaining third it is unfavorably affected. The conception that primary cases heal readily is not borne out by available facts. Tuberculous infection acts as any other infection and the best place to fight it is at the portal of entry, before it attacks and subdues the nodes. In treatment, the most active agents are those acting on the mechanics of respiration, rest in the first place. Better than pneumothorax, phrenic paralysis should be tried in cases where the base or middle lobe are involved. An extrafascial apicolysis, either alone or combined with the former, or a simple "ligamentolysis" will secure the essential collapse and prove effective in a few months under regular X-ray control. Pneumothorax cannot achieve as much. A typical case in an infant with progressive tuberculosis is reported. A ligamentolysis was followed by recovery within six months and complete normality within one year. The most favorable time for trying collapse is before ulceration develops.—*Nueva orientación terapéutica en la tuberculosis pulmonar*, M. Chapo Bortagaray, *Prensa méd. argent.*, May 30, 1947, 34: 990.—(A. A. Moll)

Bilateral Collapse Therapy.—A two-year experience with bilateral collapse therapy in the 100-odd-bed Miguel Pereira Hospital in Rio de Janeiro is reviewed. Many patients otherwise considered hopeless thus recovered. Among 890 patients treated with collapse methods, bilateral collapse had to be attempted 92 times because of excavated lesions in both lungs. A combination of pneumothorax with contralateral thoracoplasty was the most common form of bilateral collapse therapy—24 out of 92 cases—pneumothorax being tried first. Continuance of either mono- or bilateral collapse depends on the results of pleuroscopic examination which should be a routine step in every case. Typical cases are reported. For prognostic purposes the vital capacity data secured spirographically seem most significant. Among 745 pleuroscopies and intrapleural pneumonolyses only 16 (2.14 per cent) failed to show adhesions. Out of the 92 bilateral cases, 83 left the hospital with a repeatedly negative sputum. Four most successful cases of bilateral thoracoplasty are presented at length as they suggest the great possibilities of this method in the future.—*A colapsoterapia bilateral no Hospital Miguel Pereira*, R. Fernandes & J. M. Castello Branco, *Clin. fisiol.* (Rio de Janeiro), October-December, 1946, 1: 303.—(A. A. Moll)

Traumatic Initial Pneumothorax.—Previous reports have indicated that trauma to the visceral pleura is inevitable in induction of pneumothorax when using a sharp beveled needle. To ascertain if trauma, with induction of a spontaneous pneumothorax of traumatic origin, were also inevitable when using a short beveled, dull needle, a series of 29 cases is reported. A number 19 dull, short beveled pneumothorax needle was used in the anesthetized chest wall to obtain negative pressure readings on the manometer. When such readings were obtained, the needle was promptly withdrawn in 19 cases without injecting air; in 10 cases a small amount of air, averaging 100 cc., was given before withdrawing the needle. In all but 5 cases out of

the 29, a fluctuation in the negative readings was noted, suggesting that a space had already been created between the pleurae by the time the needle was attached to the manometer. The patients were then observed carefully for pain in the neck or shoulder, indicating that a pneumothorax space was being created. In such cases, an X-ray film was taken immediately; otherwise, if there were no complaints of pain, a film was taken in three hours after the procedure had been completed. Fluoroscopy was found to be unsatisfactory to detect small amounts of air in the pleural space; an expiration film was more reliable. A second film in twenty-four hours was taken on all patients. Results of these observations were that in every case a pneumothorax was present, whether or not a small amount of air had been administered. When air had been given, a larger pneumothorax space than anticipated was invariably demonstrable. In almost all cases, the amount of air in the pleural space was seen to increase during the first twenty-four hours, necessitating deflations in some cases in which extreme dyspnea was present. The amount of air present in these cases was seen to vary with the extent of the disease in the underlying lungs rather than with the type of disease. An average of 15 per cent collapse was noted in moderately extensive disease; 41 per cent in extensive involvement. Caseous infiltrations, contralateral pneumothorax and pulmonary fibrosis all seemed to play a rôle to the extent to which they diminished or excluded functioning pulmonary parenchyma. The explanation for this lies in the hypothesis that, in lungs extensively involved, the remaining functioning parenchyma suffers compensatory emphysema. The site selected for induction of pneumothorax is usually overlying these distended healthy areas and the inevitable trauma in such an area to the visceral pleural membrane allows escape of alveolar air more readily than usual since the distended alveoli retract poorly. Another factor may be in the diminished respiratory reserve of extensively involved lungs which requires the constant activity of the healthy areas, thus delaying closing of the traumatic perforation and thereby leading to progressive increase in the size of the pneumothorax cavity. Because of these findings, the conclusion is drawn that even with the use of a dull short beveled needle, the real initial pneumothorax is a traumatic one, creating a space to which air is then added. Manometric readings which show a fluctuation with the respiratory cycle, which were found to be present in 24 of the 29 cases studied, indicate that an air space is produced without the introduction of air from the outside, thus substantiating the assumption that visceral pleural trauma is inevitable in inducing pneumothorax. Four case histories showing the progression of the pneumothorax space during the first twenty-four hours, even though no air had been given.—*The Rôle of Traumatism in the Induction of Initial Pneumothorax: Further Studies, I. G. Tchertkoff & I. J. Schikoff, Quart. Bull. Sea View Hosp., January, 1947, 9: 1.*—(P. Q. Edwards)

Phrenicectomy for Hilar Cavities.—Among 19 patients with cavities in the upper lobe treated with phrenic exeresis, not one showed any appreciable benefit from the operation. In 15 other cases which had cavities apparently in the hilar region according to X-ray appearance but actually located at the apex of the lower lobe or in the middle lobe, only one instance failed to respond to this treatment. Only one patient out of 8 with lesions in other parts of the upper lobe responded to this operation. Accordingly it is recommended that hilar cavities should be localized not only by anterior films but also by lateral and oblique films and by stereoscopic films. It is always possible to determine by sufficient films if the cavity is localized at the apex of the lower or in the middle lobe on the right side. Cavities in the lower lobe or mid-lobe are best treated by primary phrenicectomy as pneumothorax is less effective in these cases. Cavities at the base of the upper lobe are better treated by pneumothorax, since these cases do not respond well to phrenic exeresis.—

Contribution au traitement des cavernes dites hilaires par la phrénicectomie, A. C. Chakar & Z. S. Kösioglu, *Presse méd.*, June 4, 1947, 33: 381.—(E. Bogen)

Pneumonolysis and Phrenic Paralysis.—Case report demonstrating the indication, in certain instances, of severing the phrenic nerve during a pneumonolysis. In this patient two large cavities were present, one of which was situated in the lower lobe. Pneumonolysis succeeded in liberating the upper lobe from all adhesions—the lower lobe, however, remained attached to the diaphragm and the posterior chest wall. It was observed through the thoracoscope that the diaphragmatic motions exerted a pull on the lesion in the lower lobe. The phrenic nerve was severed by cauterization through the thoracoscope.—*Sur un nouveau cas de section du nerf phrénique par voie pleuroscopique*, A. Meyer & A. Davy, *Rev. de la tuberc.*, 1947, 11: 220.—(V. Lcites)

Pneumoperitoneum for Pleurisy.—Exudative pleurisy is always tuberculous unless proved otherwise. According to Hofer, one case in 4 without pulmonary involvement visible in an X-ray film dies of tuberculosis, usually within a year. Forty per cent of Burrill's large series of cases developed open tuberculosis. Hayasi followed the results of exudative pleurisy in 2,321 cases and 46.8 per cent became open cases as did 33.5 per cent of Michetti's more than a thousand cases. It is certainly most necessary to find if possible some way of preventing such a large proportion of patients with pleural effusion from developing progressive pulmonary tuberculosis. P. E. Weil tried prompt aspiration replacing the fluid with air. Wolf also used this measure. The author believes that the initial infection in pleurisy spreads principally by the lymphatic channels and that only collapse therapy can block them. According to the investigations of Spengler, sediment from pleural effusions settles in the costophrenic angles and consists of cells and bacilli. Inflammatory changes as shown by thoracoscopies are always more intense near the base

of the pleural cavity when an effusion is present. As the fluid is absorbed there often remains in the costophrenic angle what appears to be a thickening of the pleura but is really a mass of cellular detritus and tubercle bacilli. The time of the absorption of the pleural fluid is a critical and dangerous period. After the fluid is gone there often remains for an indefinite time a considerable amount of this cellular infectious sediment which is mistaken for pleural thickening or a band of adhesion. According to the author, this sediment plays an important part in post-pleuritic morbid sequelae, for it always provides the bacilli which find their way into the lymphatic channels or the blood vessels. We must be especially on our guard in cases of primary infection with effusion. The author does not think that pneumothorax is always the best method of prophylactic collapse but prefers his combination of phrenic nerve section and avulsion (to paralyze the diaphragm) with pneumoperitoneum. He has employed it in a considerable number of cases with satisfactory results. He does not think it necessary to employ it in very mild cases. These he treats with bed-rest and hygienic measures. His treatment of the moderately severe cases seems quite radical.—*Traitment de la pleurésie exsudative dans le but d'éviter des suites éloignées*, G. Maurer, *Rev. belge de la tuberc.*, 1947, 38: 26.—(A. T. Laird)

Extrapleural Pneumothorax.—The author proposes the term "extrapleural substitution pneumothorax" for an operation recommended by him under certain conditions, which consists in supplementing or replacing an incomplete or ineffective pneumothorax with an extrapleural pneumothorax. The latter procedure should result in an extrapleural air space, covering all or nearly all of the area of the preceding intrapleural pneumothorax and thus exerting collapsing pressure on the pleural space, its adherent or thickened walls and the underlying lesions and cavities. In certain cases very extensive extrapleural pneumothorax would be necessary to bring this about, extending even from the apex to

the base. He has used such a procedure in about 40 cases and reports some very satisfactory results. He discusses its use in connection with basal as well as apical lesions, and goes into some detail as regards its risks and the alternative methods of treating the various conditions which he considers to be indications for its employment. The complications which frequently follow the induction of much less extensive extrapleural pneumothorax are so serious that many thoracic surgeons would not undertake the very extensive operations illustrated in the fifteen drawings which accompany the text.—*Le pneumothorax extrapleural de substitution*, P. le Foyer & G. Vallade, *Le Poumon*, May-June, 1947, 3: 11.—(A. T. Laird)

Extrapleural Pneumothorax.—A study based on the observation of 90 cases over a period of two to eight years. A detailed description is given of the operative technique, postoperative management, complications and their treatment. Good results with closure of cavities and negative sputum were obtained in 45 patients (50 per cent). Improvement with full working capacity was achieved in 12 patients (13 per cent). Unfavorable results are in part attributed to hardships during the war, insufficient sanatorium care, premature reexpansion due to evacuation from hospitals, etc. The total fatality of the operated cases was 10 per cent in nine years. Thoracoplasty following extrapleural pneumothorax is considered technically more difficult, but better tolerated by the patients because of fixation of the mediastinum. A correlation is seen between the type of lung involvement and incidence of complications; pleural complications were most frequently found if pulmonary lesions were of the disseminated hematogenous type with particular involvement of the cortical layers of the lung. As further contraindications are considered: peripheral location of cavities, giant cavities, fresh exudative processes, presence of considerable fibrosis,

extrapulmonary tuberculosis.—*Extrapleural Pneumothorax and Oleothorax in the Treatment of Pulmonary Tuberculosis*, T. N. Chupshchenko, *Probl. tuberk.*, 1947, No. 1, 26.—(V. Leites)

Extrapleural Pneumothorax.—Lower extrapleural pneumothorax is considered indicated (1) in cavities of the lower lobes after failure of intrapleural pneumothorax and phrenic paralysis, (2) as a complementary procedure in the presence of upper extrapleural pneumothorax or upper thoracoplasty in the presence of progression of the disease towards the lower lobes. The special operative difficulties of lower extrapleural pneumothorax (due to the anatomy of the fascia endothoracica) are described. The maintenance of the extrapleural space demands even more attention than in upper extrapleural pneumothorax because of the greater tendency towards obliteration and the constant presence of fluid. Replacement of air with oil has to be instituted at an early date. Lower extrapleural pneumothorax constitutes a considerable diminution of the breathing capacity and demands preoperatively a careful evaluation of the function of the contralateral lung.—*Concerning the Question of Lower Extrapleural Pneumothorax*, D. P. Muchin, *Probl. tuberk.*, 1947, No. 1, 38.—(V. Leites)

Extrapleural Pneumothorax.—Following extrapleural pneumonolysis, the authors place 50 cc. of serum containing 1,000,000 units of penicillin in the space and remove remaining air. Thereafter, air is gradually introduced, injecting 100 to 150 cc. daily until adhesion and collapse is obtained. This procedure, used on 62 patients, protects against re-collapse with extrapleural pneumothorax and prevents many of the complications ordinarily observed. Eight figures illustrate the procedure in one case of bilateral extrapleural collapse.—*Pneumothorax extrapleural lapsus progressivo*, P. Le Foyer, *Pres. Med.*, June 4, 1947, 33: 385.—(E. Bogen)

The pathogenic fungi found in the sputum are complex in nature and present marked differences in appearance and cultural characteristics. The information required for the identification of the fungus is best acquired by means of illustrations. In the present article the text has been purposely much abbreviated and the emphasis placed on the illustrations.

It is hoped that it will serve as a useful guide to the laboratory worker interested in this type of study.

COLLECTION OF THE SPUTUM

The details concerned in the collection of the sputum are of first importance and in not a few instances that have come to our attention the identification of the fungus has rested on this factor alone. The physician or some qualified person should attend to these details. The sputum should be collected shortly after the patient awakens in the morning. A morning specimen represents the pulmonary secretions accumulated during the night and, in general, is the most satisfactory one for the examination; it is also free from food particles. Before the specimen is obtained the patient is instructed to brush the teeth and to rinse and gargle the mouth and throat. Great care must be exercised to see that the sputum comes from the lungs. Avoid all specimens of saliva or nasopharyngeal secretions. Sterilized petri dishes serve best as a receptacle for the sputum which should be immediately sent to the laboratory for examination. This will prevent the multiplication of the bacteria in the sputum, an undesirable feature.

The sputum should be carefully examined with a hand lens for the presence of tiny particles or flecks from one-half to three millimeters in diameter, yellowish or gray in color, which appear denser than the surrounding sputum. In some instances the fungi can only be demonstrated in such flecks and for this reason they should be selected for the microscopic study and the inoculation of the medium.

PREPARATION OF THE SPUTUM FOR MICROSCOPIC STUDY

Select, by preference, several of the above mentioned flecks and place on a clean glass slide, add one or two drops of 10 per cent sodium hydroxide and mix thoroughly. Place a cover glass over the preparation and, after an interval of three to five minutes, examine the preparation for fungi with a low and a high powered lens in a subdued light. If fungi are not found by this method it is advisable to concentrate the sputum. Place the sputum in a 50 cc. centrifuge tube and add approximately twice the amount of 4 per cent sodium hydroxide. Place the tube in boiling water for approximately five minutes, stirring the contents occasionally with a glass rod. Centrifuge for twenty minutes at high speed, decant the supernatant fluid and resuspend the sediment in 2 cc. of distilled water. Put one loopful of the mixture on a clean glass slide and place a cover glass over the preparation. The microscopic study of the unstained preparation of the sputum may suffice for the identification of the offending fungus. However, it is advisable to confirm the microscopic findings by cultural

methods. The fungi are killed at the time the sputum is concentrated and therefore the material is not serviceable as an inoculum.

PREPARATION OF MEDIA FOR THE CULTIVATION OF FUNGI

The nutritional demands of the fungi under consideration are different and for this reason several media are employed for their cultivation.

Sabouraud's Agar Medium

Sabouraud's agar is the standard medium for the isolation of fungi and is prepared as follows:

Dextrose.....	40.0 g.
Peptone.....	10.0 g.
Agar.....	20.0 g.
Distilled water.....	1000.0 cc.

Heat over steam bath or in autoclave until the ingredients are completely dissolved. Adjust the medium to a pH 5.2 to 5.5 by the addition of normal hydrochloric acid. Dispense the medium in lots of 50 to 100 cc. in glass bottles; sterilize in autoclave for fifteen minutes at 15 pounds pressure. Place the medium in the refrigerator for future use. The medium preparatory to use is melted in a steam bath or autoclave, poured in petri dishes and allowed to solidify.

Dextrose Yeast Extract Medium

Dextrose.....	5.0 g.
Sodium chloride.....	1.7 g.
Yeast extract, Difco.....	0.5 g.
Distilled water to make.....	200 cc.

Adjust the undiluted medium to pH 4 with normal hydrochloric acid. The medium is dispensed in test tubes in lots of 5 cc. and sterilized in the autoclave for fifteen minutes at 15 pounds pressure. The medium is ready for use on cooling.

Nutrient Agar

Meat extract.....	3 g.
Peptone.....	10 g.
Sodium chloride.....	5 g.
Agar.....	25 g.
Distilled water.....	1000 cc.

Dissolve ingredients by heating in steam bath or autoclave. Adjust the medium to pH 7.4. Dispense in 100 cc. lots and sterilize by autoclaving for fifteen minutes at 15 pounds pressure. The final reaction should be pH 7.2.

Dextrose Blood Agar

Nutrient agar.....	100 cc.
Blood.....	5 to 10 cc.
Dextrose, 20 per cent solution.....	5 cc.

The agar base is melted and then cooled to 45°C. The sterile dextrose solution and blood are added, the contents gently mixed and poured into petri dishes. After solidification, and following the inoculation with sputum, the plates are incubated under aerobic and anaerobic conditions at a temperature of 37°C. The colonies may first appear only after a lapse of two or three weeks. Sabouraud's is an excellent medium for the cultivation of fungi. However, it has one disadvantage in that it permits the growth of many bacteria commonly found in the sputum and one or more transplants may be required before the fungus is isolated in pure culture. This obstacle is overcome with dextrose yeast extract medium. It is also a medium that can be readily prepared and, therefore, can be utilized with advantage for the initial inoculation. The inoculated tubes should be incubated at 37°C. and inspected daily over a period of at least seven days. If growth is present it should be transplanted to Sabouraud's medium in order to observe more closely the development and the appearance of the colonies. If no colonies are observed a specimen of fresh sputum should be inoculated on glucose blood agar and cultivated under aerobic and anaerobic conditions at a temperature of 37°C.

SLIDE CULTURE METHOD

By this procedure one may witness the development and multiplication of the fungus and by this means alone may the fungus at times be identified. A few cubic centimeters of melted Sabouraud's agar are poured on a clean 2 x 3 inch glass slide, allowed to solidify and the surface inoculated with a loopful of sputum, or preferably with a culture grown in dextrose yeast extract. A clean, No. 1 cover glass, somewhat smaller than the glass slide, is placed over the surface of the medium. The cover glass is rimmed with vaseline, allowing a small opening at one end for the entrance of air and then incubated at 37°C. The prepared glass slide should be kept moist by placing it in a petri dish lined with a thin layer of moist cotton.

THE IDENTIFICATION OF THE FUNGUS

The various component parts of the fungus with their descriptive terms are somewhat difficult for the beginner to master. The illustrations of the component parts, plate II, should be helpful in this respect.

The distribution of the colonies, their size, shape and color should be noted as well as the outline of the colony and whether the surface is smooth and non-filamentous, or rough and filamentous.

Microscopic examination: Prepare an unstained slide preparation of the colony as described above. The identification of the fungus is based on the appearance of the mycelium together with the location, the number, size and appearance of the spores. Look for yeast-like budding cells and mycelia which may be septate or nonseptate, or of the racquet form. Note the presence or absence of spore heads, arthrospores and chlamydospores. It is important to bear in mind, in making comparisons, that the colony should conform to the age stated in the text for the illustrations. In some instances the size and the ap-

pearance of the colony may vary markedly with age. In making a microscopic comparison the same magnification should be used as stated in the text. The actinomyces is the only pathogenic fungus encountered in the sputum which requires a gram stain. Owing to the minute size of this microorganism, the preparation should be examined with the oil immersion lens. The recovery and identification of the pathogenic fungus from the sputum should be confirmed on several occasions, a safe and most excellent rule in mycotic diseases of the lungs.

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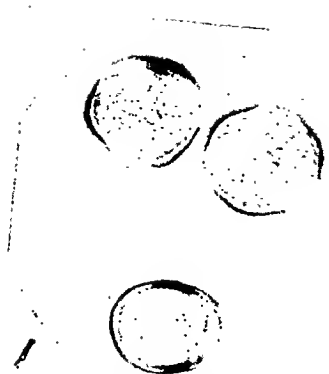
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PLATE I

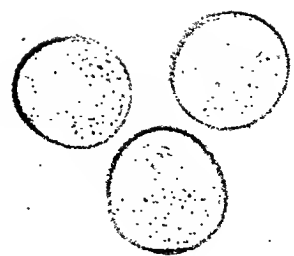
ILLUSTRATIONS OF STRUCTURES THAT RESEMBLE
FUNGI FOUND IN SPUTUM

The structures resembling fungi illustrated in PLATE I are encountered in the examination of sputum and may prove confusing.

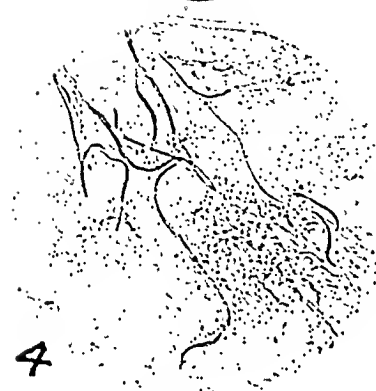
- FIG. 1. Pollen, timothy. $\times 800$.
 FIG. 2. Pollen, maple. $\times 800$.
 FIG. 3. Cotton fibers. $\times 100$.
 FIGS. 4 and 5. Elastic tissue. These are slender, highly refractile, wavy fibrils of uniform diameter and with double contour. They may appear as single strands or in bundles and frequently show an alveolar arrangement. Their ends are often frayed or split. $\times 200$.
 FIG. 6. Fat cells. $\times 800$.
 FIGS. 7 and 8. Myelin globules. Colorless globules occurring in a variety of sizes and bizarre forms. $\times 800$.
 FIG. 9. Bacterial colony. Frequently found in sputum as small granules, gray or yellowish in color. They consist of a mass of either cocci or bacilli. $\times 400$.
 FIGS. 10 and 11. Asbestos bodies. May occur as single structures or in small bundles and have a yellowish color. $\times 800$.
 FIG. 12. Wool fiber. $\times 100$.



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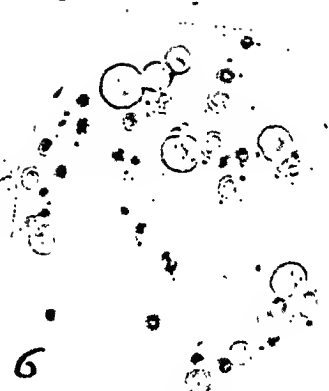
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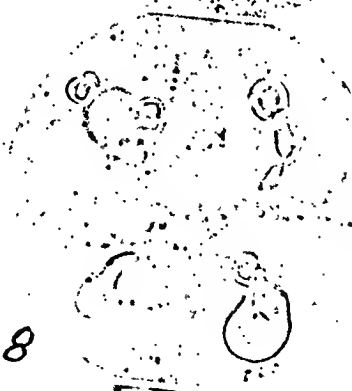
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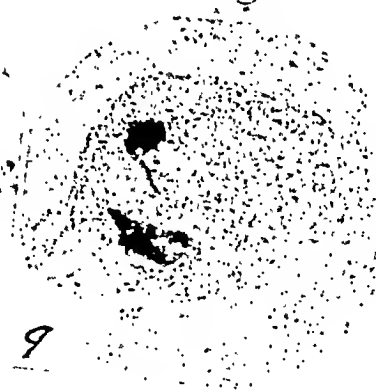
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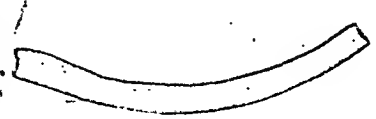
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PLATE I

PLATE II
ILLUSTRATIONS OF THE COMPONENT PARTS OF THE FUNGUS
TOGETHER WITH THEIR DESCRIPTIVE TERMS

- FIG. 1. Thallus—or colony.
 FIG. 2. Hypha—one of the filaments.
 FIG. 3. Mycelia—a collection of hyphae.
 FIG. 4. Mycelia—septate, having subdivisions of hyphae.
 FIG. 5. Mycelia—non-septate, hyphae without subdivisions.
 FIG. 6. Sporehead (*Aspergillus*)
 (a) Conidiophore, mycelial stalk bearing conidia.
 (b) Vesicle, the swollen portion of the conidiophore.
 (c) Conidia, the spores.
 FIG. 7. Endospores—spores formed within the parent cell.
 FIG. 8. Blastospores or budding forms—spores developed by budding from the side of a parent cell.
 FIG. 9. Sporophore—that part of the hypha which bears the spores.
 FIG. 10. Arthrospores—segmentation of the hypha into chains of cells.
 FIG. 11. Ascospores—spores formed within a sac called an ascus. The spores are limited in number to two, four or eight, depending on the species producing them.
 FIG. 12. Chlamydospores—a swollen portion of the hypha. A resting spore which may be terminal, lateral or develop along the hypha.
- Detailed descriptions of the component parts of the fungus are contained in standard text-books on the subject.

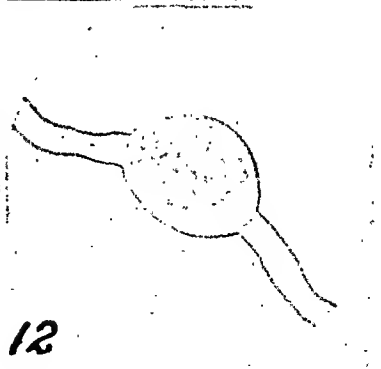
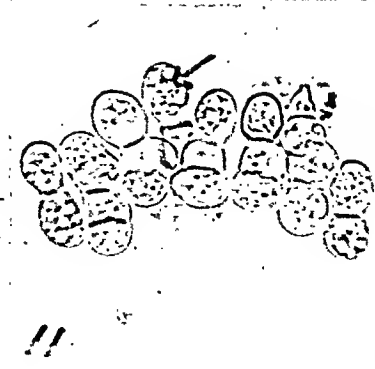
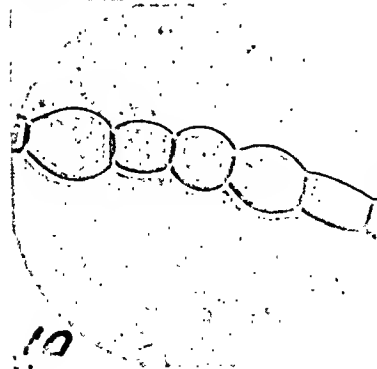
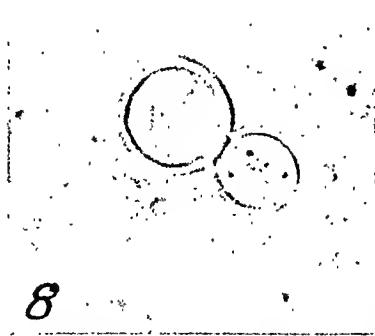
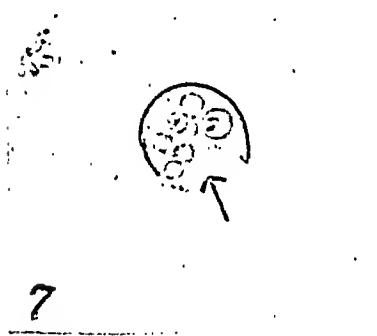
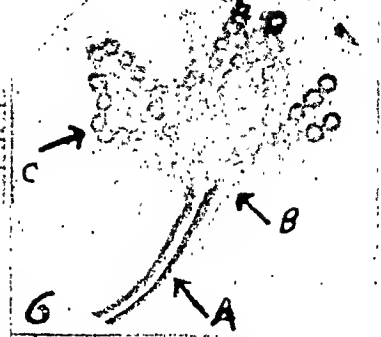
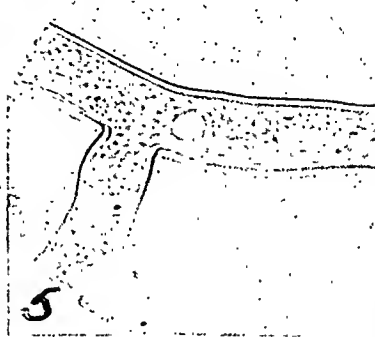
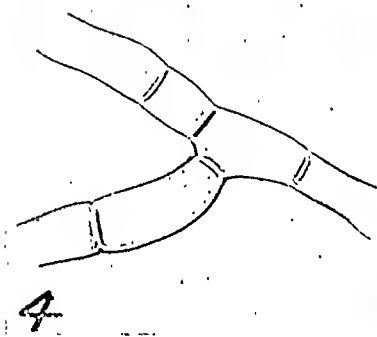
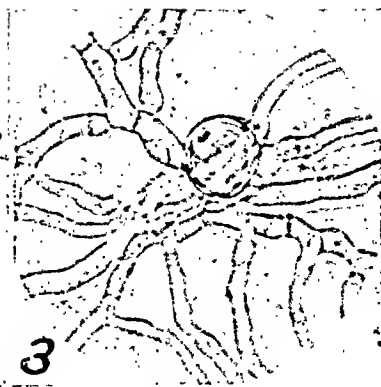
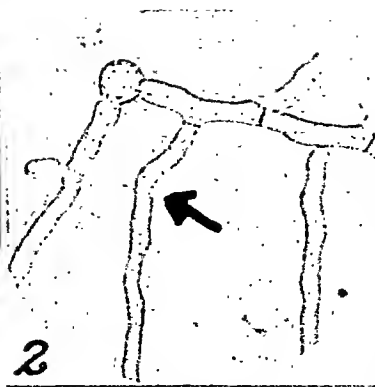
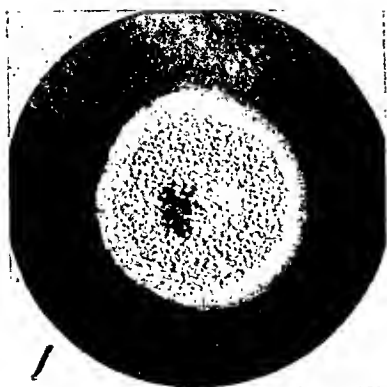


PLATE II

PLATE III

ACTINOMYCES

Actinomyces bovis gives rise to the characteristic sulphur granules, gray or yellowish in color, and varying in size, usually less than 1 mm. in diameter. When crushed between a glass slide and cover glass and examined microscopically they are found to consist of numerous smaller granules or colonies (figure 1) composed of a mass of mycelial filaments approximately 1.0 μ in diameter (figures 6, 7, 8). Around the periphery of some of these granules the filaments are arranged radially with their ends expanded into club-like forms, 10 to 20 μ in length and 5 to 8 μ in width (figures 2, 3, 4). Granules without clubbed ends may also be seen in the same preparation (figure 5). Gram stains made from crushed granules show the central filaments to be gram-positive, whereas the clubbed ends are gram-negative (figures 6, 7, 8).

Actinomyces bovis is an anaerobic organism which grows best at 37°C. The addition of glucose and blood to the medium facilitates the initial growth which varies from three to ten days before the colonies are visible. The colonies are small, round and discrete, and slowly increase in size. The surface may be finely granular or nodular and is white in color (plate IV, figure 9).

The aerobic actinomyces grow well on Sabouraud's agar medium. The colonies may be white or various shades of yellow to orange. They may develop irregular folds and concentric rings and may become covered with short aerial hyphae, assuming a chalky appearance.

In meat infusion broth both anaerobic and aerobic actinomyces develop slowly. Growth appears in from three to ten days, first noted in the bottom of the tube as small, fluffy or granular colonies which may be adherent to each other. Surface growth may be a wrinkled pellicle, at times pigmented.

Microscopically, the organisms are gram-positive pleomorphic branching filaments which often stain irregularly (figure 10). The anaerobic type is non-acid-fast, while the aerobic type may or may not be acid-fast.

Actinomycotic granules in hematoxylin-eosin stained preparations are best observed in the abscessed areas of the lung. The granules vary greatly in size. The central portion stains a deep blue color while the outer edge, or the clubbed ends, at times not prominent, stain pink (plate V). The granules, when stained by Gram's method are seen to consist of an interlacing network of gram-positive filaments, approximately 1 μ in diameter, and having a radial arrangement (plate IV, figure 11). By careful search one may observe variable sized clusters of gram-positive filaments. At times only a few short filaments are present while the larger clusters may consist of numerous filaments. Hematoxylin-eosin stained sections fail to reveal these small granules which may be overlooked unless stained by Gram's method.

FIG. 1. Unstained slide preparation of an *Actinomyces bovis* granule in sputum. When crushed between a glass slide and cover glass, numerous smaller granules are seen. Some of these show typical clubbed ends while others do not. $\times 50$.

FIG. 2. Granule with clubbed ends. $\times 200$.

FIG. 3. Another granule with clubs. $\times 400$.

FIG. 4. Edge of granule showing clubs in detail. $\times 800$.

FIG. 5. Granule without clubbed ends. $\times 200$.

FIGS. 6, 7 and 8. Crushed granule stained by Gram's method showing gram-positive pleomorphic filaments. Figure 6 shows a clubbed end with attached filament; figure 7 a beginning club at the end of a long filament; while a detached club is seen in figure 8.

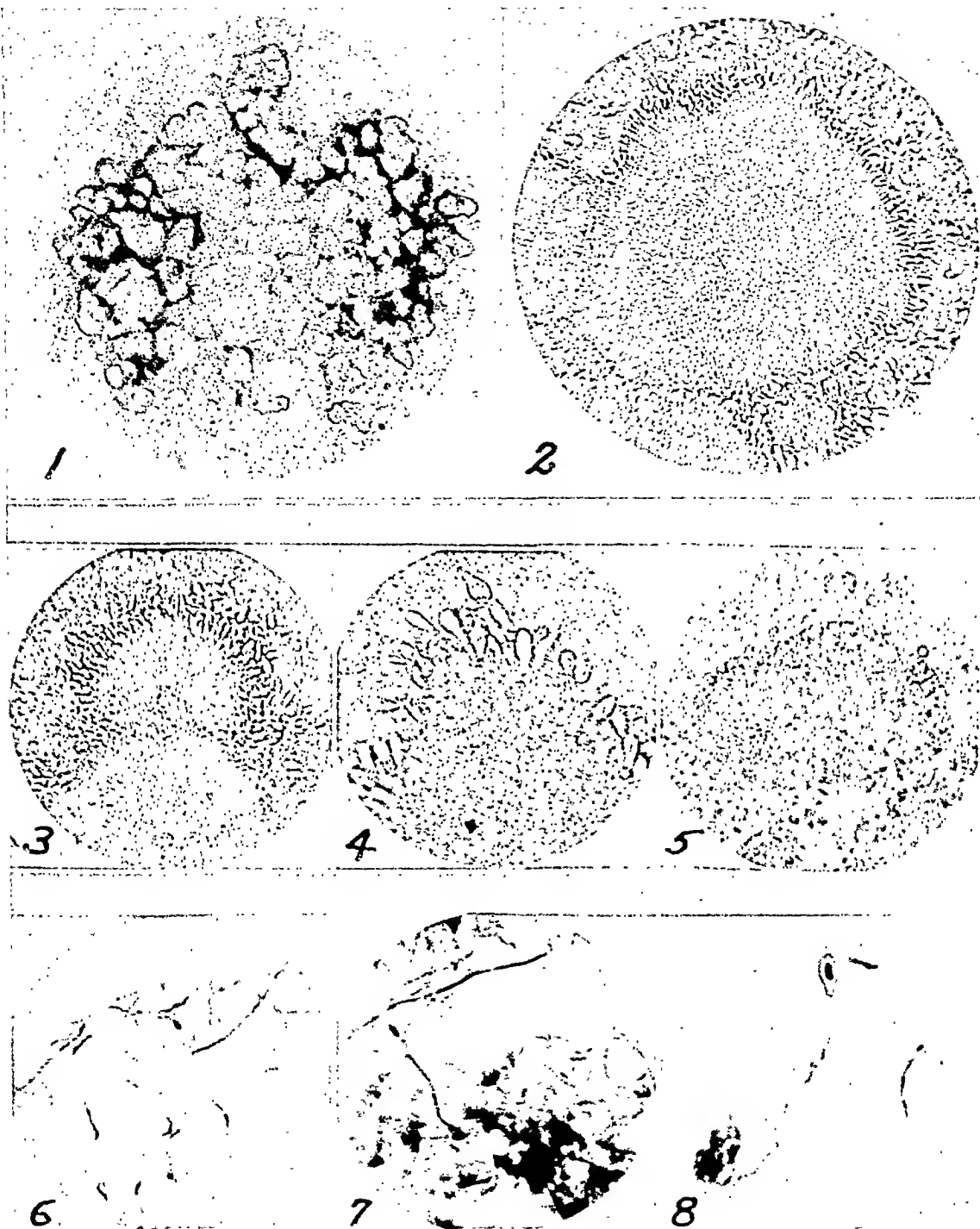


PLATE III

PLATE IV

ACTINOMYCES

- FIG. 9. *Actinomyces boris* colony grown anaerobically on dextrose blood agar, seven days at 37°C. $\times 10$.
- FIG. 10. Gram stain preparation made from a colony grown anaerobically on dextrose blood agar, seven days at 37°C. $\times 1000$.
- FIG. 11. Edge of granule in lung stained by Gram showing gram-positive branching filaments. $\times 1000$.
- FIG. 12. Edge of granule in lung with clubbed ends. Hematoxylin-eosin stain. $\times 800$.

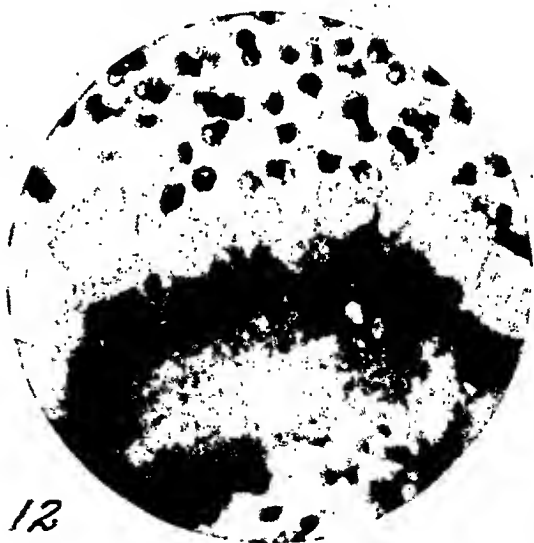
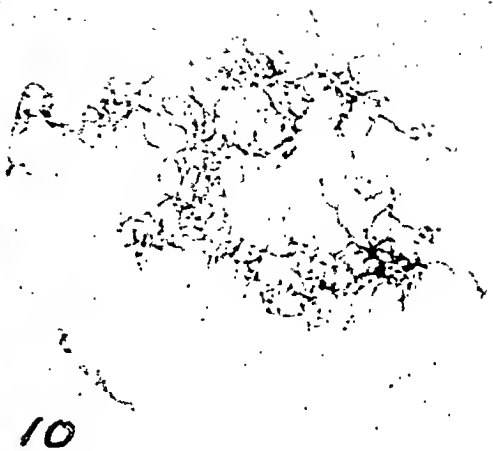
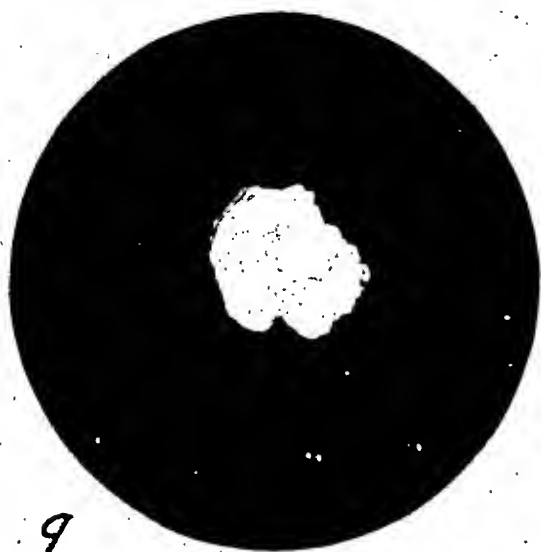


PLATE IV

JOSEPH M. KURUNG

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PLATE V

Kodachrome illustration of an actinomyces granule in lung. $\times 200$.

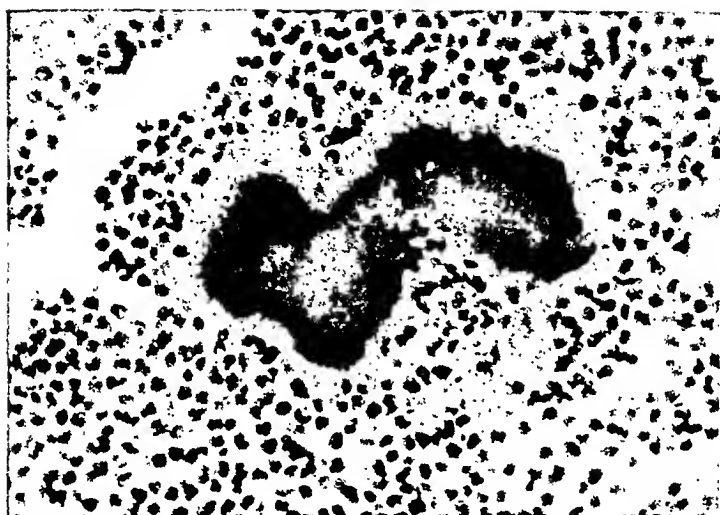


PLATE V

PLATE VI

COCCIDIOIDES IMMITIS

On microscopic examination of the fresh sputum the microorganisms appear as round, doubly-contoured spherules, varying from 5 to 70 μ in diameter. They may be seen in different stages of development. The young cells have a thin wall and contain finely granular protoplasm, while the older cells have a thicker wall and contain large numbers of small round endospores (plate XI, figure 2). Other cells appear as mere shells, only the wall remaining, at times with a few scattered spores near the ruptured cell.

Growth appears in two to ten days. On Sabouraud's agar medium, the colonies appear as small, white, fuzzy plaques, gradually becoming larger and covered with an abundance of white, aerial hyphae (plate XI, figure 2A). The color changes to brown with age. Microscopically, there is an abundance of branching, septate mycelium, with hyphae 2 to 4 μ in diameter, and giving rise to racquet mycelium and chlamydospores, 4 to 10 μ , and arthrospores 3 to 6 μ in diameter (plate XI, figure 2B).

In dextrose-yeast extract medium, the colonies appear as small, white, fluffy snowflake-like colonies at the bottom of the tube, the medium remaining clear. Microscopically, each colony appears as a mass of tangled, branching septate mycelium with an abundance of chlamydospores and arthrospores.

Plate VI sections of the lung stained with hematoxylin and cosin show the organism in various stages of development. They vary in size from 5 to 70 μ in diameter from the thin-walled younger cells to the large thick-walled double-contoured cells filled with endospores (plate VI, figures 1 to 7). The younger cells tend to stain irregularly; in some of the cells only a narrow border just beneath the capsule is stained blue, while in others the cell stains diffusely (figures 1 and 6). Spherules with a ruptured border (figure 3) are frequently observed as well as clumps of endospores without the capsule (figure 4). Spherules in giant cells may also be present (figure 7). At times peripheral spines may be observed surrounding a spherule. Spherules without endospores are almost identical with the nonbudding forms of blastomyces. However, the presence of the characteristic endospore-forming spherules and the absence of budding forms are helpful in identification.

- FIG. 1. *Coccidioides immitis* spherules in various stages of development. Lung node. $\times 400$.
- FIG. 2. Mature spherule containing a large number of endospores. Lung. $\times 800$.
- FIG. 3. Ruptured spherule. Lung. $\times 800$.
- FIG. 4. A nest of freshly liberated endospores. Lung. $\times 800$.
- FIG. 5. Early development of endospores. Seen in various stages of growth. Lymph node. $\times 400$.
- FIG. 6. Spherules in a later stage. Lymph node. $\times 400$.
- FIG. 7. Two giant cells each containing five young spores. Lymph node. $\times 400$.

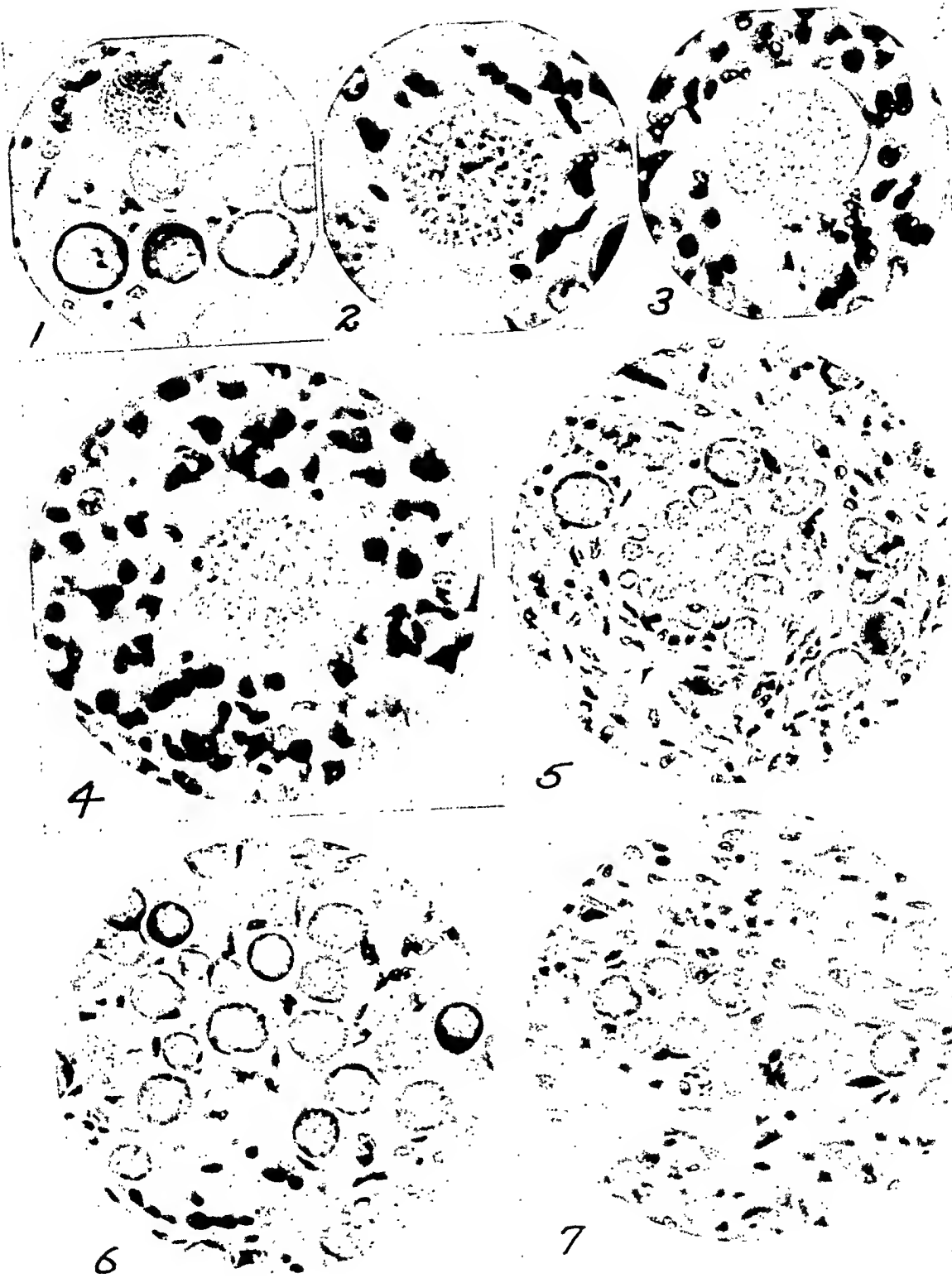


PLATE VI

PLATE VII

BLASTOMYCES

On microscopic examination of the fresh sputum the organisms appear as round or oval cells, 10 to 15 μ in diameter, having a well-marked, highly refractile, double-contoured capsule; they are found singly or in small clusters (figures 1, 2, 3). The protoplasm is granular and may contain one or more refractile vacuoles. Budding forms are always present. No mycelium occurs in sputum or pus.

Both dextrose blood agar and Sabouraud's agar media should be used. Colonies appear in three or seven days or later. On dextrose blood agar at 37°C. the colonies are yellowish-brown, wrinkled and similar to those produced by tubercle bacilli (plate XI, figure 1A). They are friable and easily broken into small fragments on the slide. Aerial hyphae are not present. Microscopically, one observes round or oval budding forms, similar to those found in sputum or pus. The cell wall is thick and highly refractile (plate XI, figure 1C).

On Sabouraud's medium the organisms appear as small, white, fuzzy colonies which gradually increase in size and become covered with age. Microscopically these are branching, septate, mycelia, 3 to 4 μ in diameter, to which are attached terminal and lateral conidia, 6 to 8 μ in diameter (plate XI, figure 1D).

In liquid media, such as meat-infusion broth, the organisms grow as tufted masses in the bottom of the tubes, the medium remaining clear. As the culture becomes older, a white fluffy pellicle is formed. Microscopically these organisms are similar to those grown on Sabouraud's medium.

Blastomyces in hematoxylin-eosin stained sections of lung are seen as round or slightly oval cells, 8 to 25 μ in diameter, with a thick wall and a highly refractile, double-contoured capsule (plate VII, figures 4, 5, S). Budding cells are always present (figure 6). The organisms may be observed lying free (figure S) or in groups (figures 4 and 5) and are frequently seen in giant cells (figure 7). The body of the cells stain light blue throughout while the capsule remains unstained.

Figs. 1, 2 and 3. Unstained slide preparation of sputum showing the characteristic thick-walled, double-contoured, budding blastomyces spores. $\times 800$.

Figs. 4 and 5. Blastomyces spores in lung. $\times 400$.

Fig. 6. Budding blastomyces spores in lung. $\times 400$.

Fig. 7. Blastomyces spore in giant cell; in lung. $\times 400$.

Fig. 8. Typical thick-walled spore; in lung. $\times 800$.

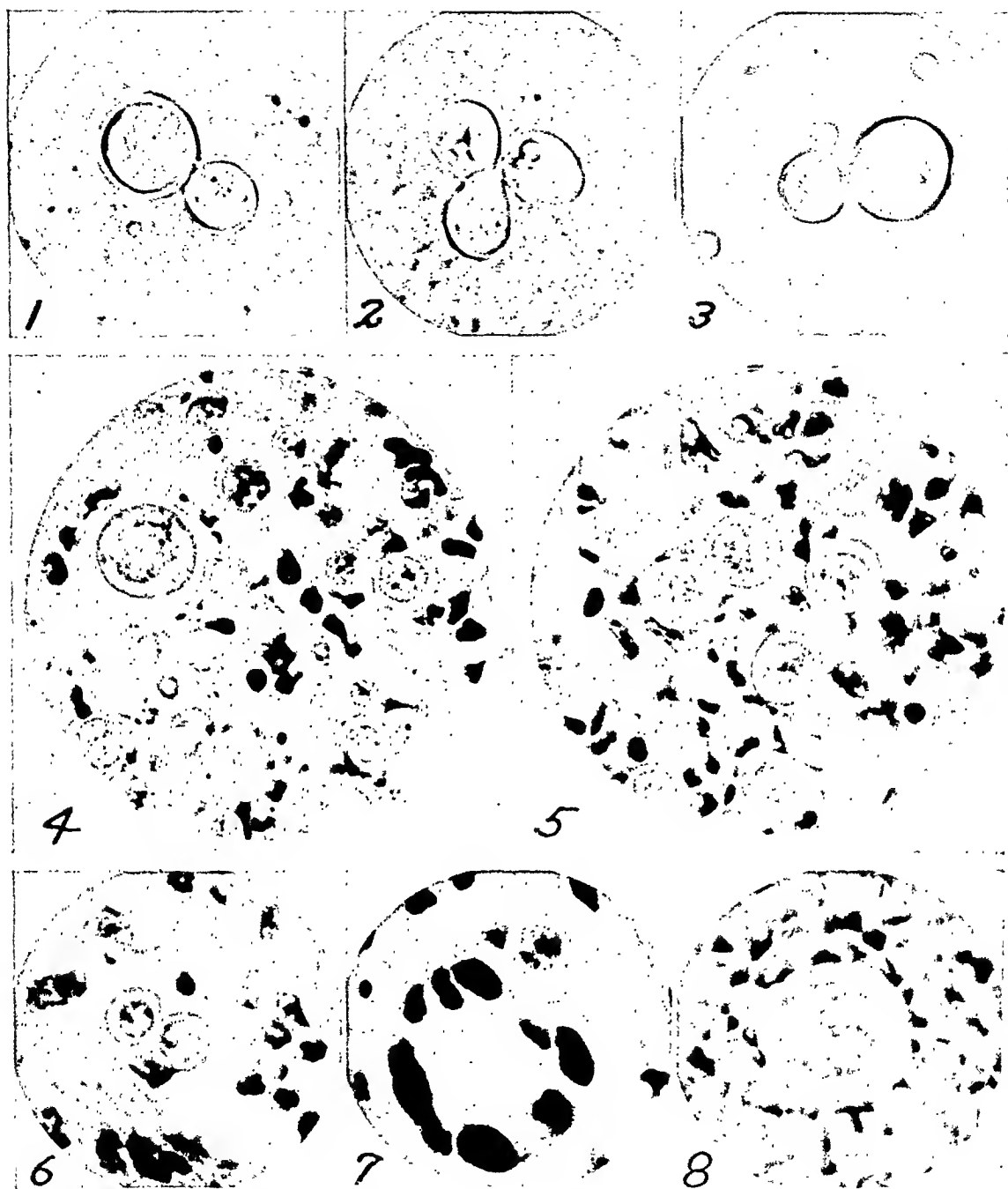


PLATE VII

PLATE VIII

HISTOPLASMA CAPSULATUM

On microscopic examination of the fresh sputum the microorganisms appear as round or oval yeast-like cells, usually with one budding cell attached, measuring 2 to 4 μ in diameter, and surrounded by a thin, well-defined refractile capsule. A large vacuole and a granule are frequently present within the cytoplasm.

There are two different forms of this fungus: the yeast-like form as seen in pus, tissue and when grown on dextrose blood agar; and the mycelial form which is seen when grown on Sabouraud's agar medium.

Growth is slow, usually requiring four to ten days at 37°C. before the colonies become visible. On Sabouraud's agar medium the colonies are white and cottony, slowly increasing in size while the aerial hyphae become more abundant (figure 1). Older cultures change from white to a light brown color. Microscopically, this microorganism gives rise to septate, branching mycelia, 2 to 4 μ in diameter. Round or pyriform spores, 3 to 10 μ in diameter, can be seen on short lateral branches along the hyphae. The characteristic identifying structures are the large, thick-walled, round or pyriform tuberculated chlamydo-spores, varying in size from 7 to 20 μ in diameter (figure 2).

On dextrose blood agar, the growth appears as small pasty colonies. Microscopic preparations made from these colonies exhibit small, round or oval yeast-like cells, 2 to 4 μ in diameter, similar to those found in sputum. Budding forms are present and a large granule and vacuole may be seen within the cell.

In hematoxylin-eosin stained sections of lung the organisms appear as small oval bodies, 2 to 4 μ in diameter, surrounded by a halo or capsule. They are found intracellularly in endothelial phagocytes. The central portion of the organism stains blue while the capsule remains clear (figures 3 and 4).

FIG. 1. Colonies of *Histoplasma capsulatum* on Sabouraud's agar, nineteen days at 37°C. $\times 6$.

FIG. 2. Unstained slide preparation made from colony grown on Sabouraud's agar, nineteen days at 37°C. $\times 800$.

FIGS. 3 and 4. Hematoxylin-eosin stained section of lung showing the organisms in endothelial cells.

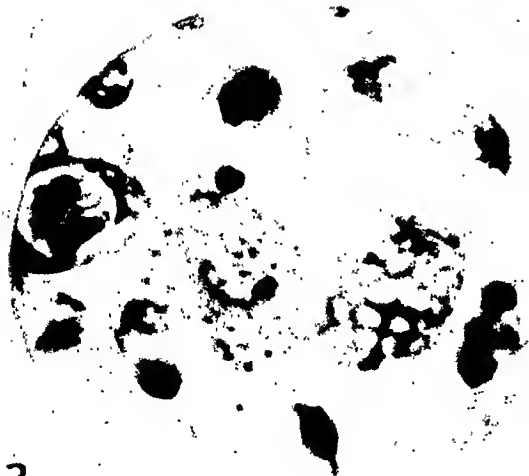
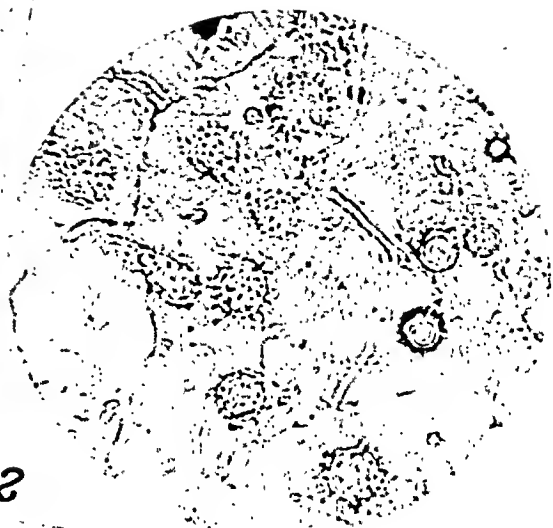


PLATE VIII

PLATE IX

CRYPTOCOCCUS

In fresh sputum the microorganisms appear as spherical cells with a thick-walled capsule, ranging in size from 5 to 15 μ in diameter. The protoplasm may contain one or more refractile granules and vacuoles. Budding forms are always present. Mycelial forms are absent.

On Sabouraud's agar medium after forty-eight to seventy-two hours' incubation, the colonies appear round, smooth, shiny and cream-white in color. They become confluent and yellowish with age. No mycelium ever develops (plate XI, figure 4A). In dextrose-yeast extract medium, growth forms a slight turbidity with a fine sediment. Pellicle and pasty ring on surface are absent.

Microscopically, the microorganisms are seen as spherical cells with well developed capsules, 5 to 10 μ in diameter (plate XI, figure 4B and plate IX, figure 1). The protoplasm is finely granular and the larger cells may contain one or more vacuoles. Budding forms are always present.

FIG. 1. Unstained slide preparation made from colony grown on Sabouraud's agar, five days at 37°C. $\times 800$.

FIG. 2. India ink preparation made from colony grown on Sabouraud's agar, five days at 37°C. $\times 800$.

SPOROTRICHUM

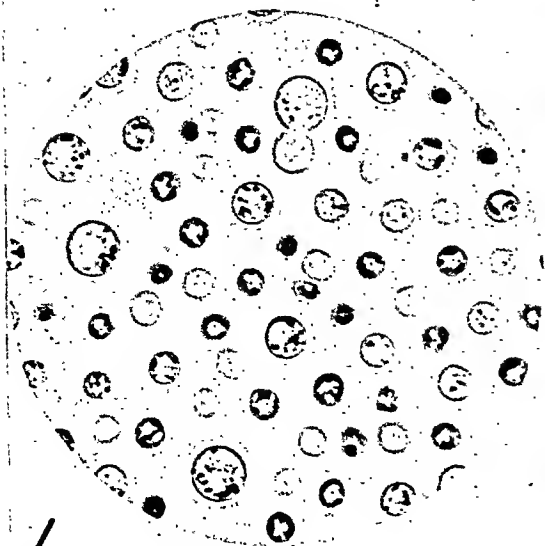
In fresh sputum the microorganisms are seen as oval or cigar-shaped bodies, from 2 to 4 μ in length and from 1 to 3 μ in width, found singly or in small clusters. They are frequently seen within pus cells. The protoplasm is finely granular and the cell surrounded by a thin capsule. The organisms resemble short, thick bacilli.

On Sabouraud's agar medium growth appears in three to ten days as white, pinhead-sized colonies which soon become surrounded by a finely-rayed fringe. Later the colonies increase in size, become convoluted, wrinkled and penetrate the medium (plate IX, figure 3). They may coalesce. Older cultures become brown to black. In dextrose-yeast extract medium growth develops slowly as small, white, fluffy colonies at the bottom of the tube, the liquid remaining clear. The colonies gradually become larger and form a thick membrane on the surface.

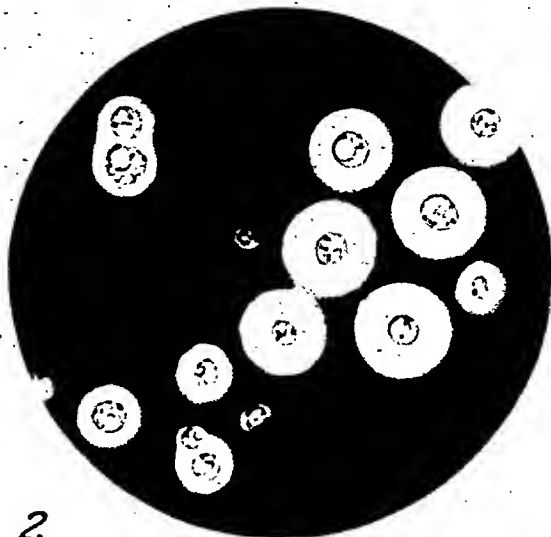
Microscopically these microorganisms are seen as branching, septate mycelium, about 2 μ in diameter. The spores, 3 to 5 μ in diameter, are single or grouped, and develop laterally along the length of the filaments, usually terminating them (plate IX, figure 4).

FIG. 3. Sporotrichum colony grown on Sabouraud's agar, five days at 37°C. $\times 4$.

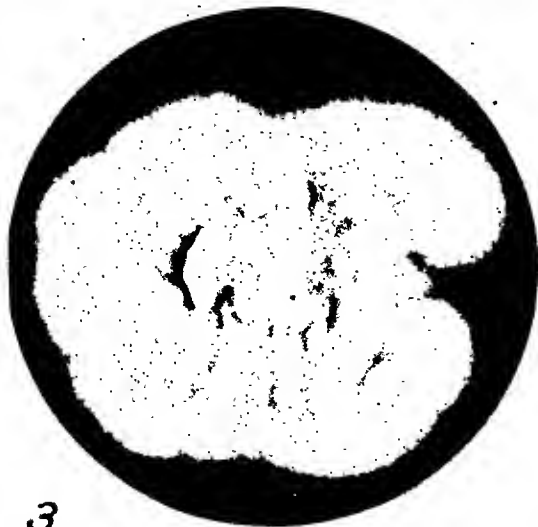
FIG. 4. Unstained slide preparation made from colony grown on Sabouraud's agar, five days at 37°C. $\times 800$.



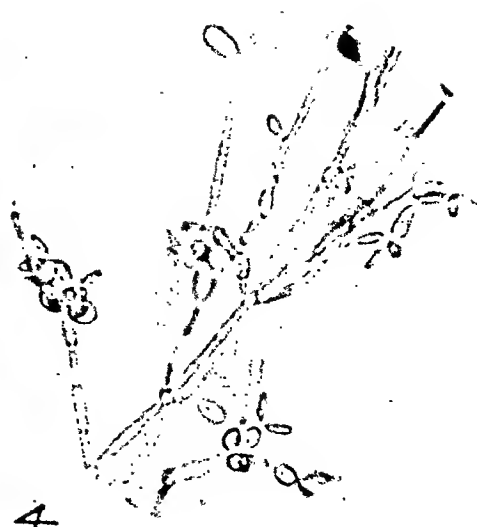
1



2



3



4

PLATE IX

PLATE X

GEOTRICHUM

In fresh sputum the organisms are seen as spherical cells, 4 to 5 μ in diameter, with a thin, double-contoured membrane. The protoplasm is finely granular and may contain a few large vacuoles.

On Sabouraud's agar medium growth appears within twenty-four to forty-eight hours. The colonies are small, white and fuzzy. They rapidly increase in size and have a characteristic radiating appearance (figure 1). These colonies are membranous and adherent to the medium. Color is white; older cultures may become yellow to amber. Dextrose-yeast extract medium becomes cloudy. Pellicle and heavy flocculent deposits are formed. Older cultures show a thick filamentous growth on the surface.

Microscopically the microorganisms exhibit septate mycelium, 3 to 7 μ in diameter, spherical, ellipsoid or cylindrical in appearance, and vary in size from 4 to 9 μ in diameter and 5 to 20 μ in length (figure 2).

FIG. 1. *Geotrichum* colonies grown on Sabouraud's agar, four days at 37°C. Actual size.

FIG. 2. Unstained slide preparation made from colony grown on Sabouraud's agar, four days at 37°C. $\times 800$.

ASPERGILLUS

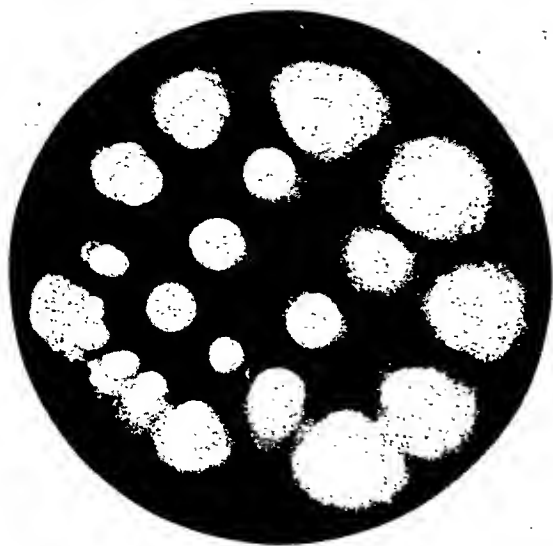
In fresh sputum these microorganisms are seen as round or slightly oval bodies, 2 to 3 μ in diameter, and occasionally as branching septate mycelial filaments.

On Sabouraud's agar medium growth appears within twenty-four to forty-eight hours. The colonies are small, white and fuzzy. These rapidly increase in size and soon coalesce to form larger colonies (figure 3). The color of the growth, which may be green, yellow, brown or black, varies with the particular species cultured. *Aspergillus fumigatus* is the species most commonly isolated from cases resembling pulmonary tuberculosis. This species has a dark green velvety appearance on culture media. It is important to point out at this time that many saprophytic species of aspergilli are—along with the *Mucor* and *Penicillium*—the most common laboratory contaminants to be encountered in this type of work. Differential description of the many species of aspergilli can be found in the book *The Aspergilli* by Thom and Church. There are excellent illustrations of contaminating fungi found on media in *The Manual of Clinical Mycology* by Conant, Martin *et al.* In dextrose-yeast extract medium, the organisms develop in the bottom of the tube as a small filamentous mass. This gradually increases in size until growth appears on the surface of the medium forming the characteristic growth of aspergilli.

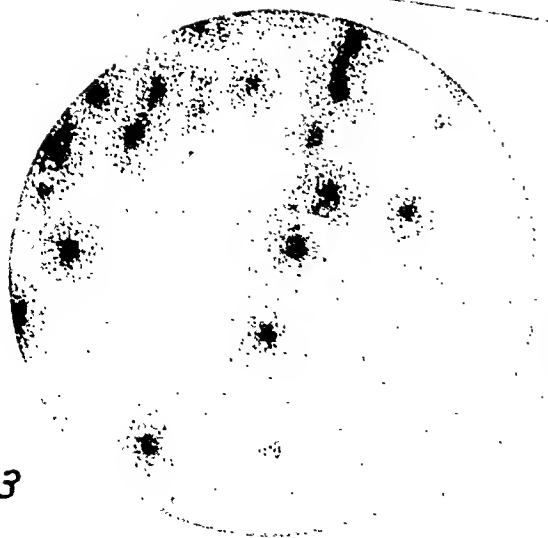
Microscopically these organisms appear as branching, septate mycelium, 2 to 5 μ in diameter. Conidiophores, which arise from large and prominent foot cells, along the mycelium, terminate in a swollen portion called the vesicle. From the latter there are given off a number of small stalks or sterigmata which in turn bear the chain of rounded conidia (figure 4). The arrangement of these component parts presents a compact mass of spores and these elements together serve as an aid in identifying the fungus.

FIG. 3. Colonies of *Aspergillus* grown on Sabouraud's agar, forty-eight hours at 37°C. Actual size.

FIG. 4. Unstained slide preparation of *Aspergillus* grown on Sabouraud's agar, forty-eight hours at 37°C. Note the spore head in the centre of the field, surrounded by conidia and mycelial filaments. $\times 800$.



2



3

4



PLATE X

PLATE XI *Cryptococcus* **APPEARANCE OF BLASTOMYCES, COCCIDIOIDES IMMITIS, CANDIDA ALBICANS** FOR COMPARATIVE STUDY

Candida albicans ×800.

Fig. 4. Unstained slide preparation of *Cryptococcus*. ×800.

Fig. 4A. Colonies of *Cryptococcus* grown on Sabouraud's agar for five days at 37°C. Actual size.

Fig. 4B. Unstained slide preparation made from colony described in figure 4A. ×800.

Fig. 3. *Candida albicans* in sputum. ×800.

Fig. 3A. Colonies of *C. albicans* grown on Sabouraud's agar, four days at 37°C. Actual size.

Fig. 3B. Unstained slide preparations made from colonies described in figure 3A.

In fresh sputum, the microorganisms are seen as round or oval, and occasionally elongated cells, 2 to 5 μ in diameter, singly or in pairs, or in small clusters. Budding forms and short strands of mycelium, at times branches, may be present. A small nucleus within the cell is frequently seen. On Sabouraud's agar medium growth appears within twenty-four to forty-eight hours. The colonies are round, smooth and elevated, and may develop a coarse or fine mycelial fringe which penetrates into the medium. The color may be white, gray or cream. The colonies have a pasty consistency and a strong yeast-like odor. On dextrose-yeast extract medium the solution becomes cloudy and a heavy flocculent deposit with a pasty ring and bubbly surface may form. In other cases, the medium may become cloudy with a fine layer of cells at the bottom of the tube. Microscopically, the organisms are seen as round or oval cells, varying in size from 3 to 9 μ in diameter, with numerous budding forms present. Occasional elongated cells connected to one or more round or oval cells are seen. Large vacuoles and granules within the cells are often present.

Fig. 2. Ruptured *Coccidioides immitis* spherule containing many endospores in sputum. ×800.

Fig. 2A. *Coccidioides immitis* colonies on Sabouraud's agar, seven days at 37°C. Actual size.

Fig. 2B. Unstained slide preparations made from colony described in figure 2A showing chains of arthrospores and quiet mycelium. ×800.

Fig. 1. Blastomycetes spores in sputum. ×800.

Fig. 1A. Dry wrinkled type of colony grown on dextrose blood agar, twelve days at 37°C. ×6.

Fig. 1B. Woolly type of colony grown on Sabouraud's agar, twelve days at 37°C. Actual size.

Fig. 1C. Unstained slide preparation made from colony described in figure 1A, showing thick-walled, double-contoured budding cells. ×800.

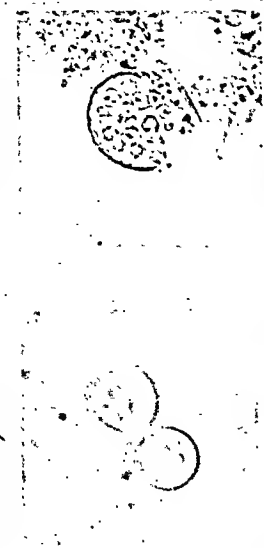
Fig. 1D. Unstained slide preparation made from colony described in figure 1B showing filamentous growth with small round lateral spores. ×800.

Blastomyces

Coccidioides immitis

Candida albicans

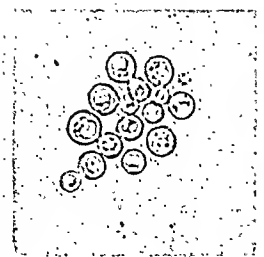
Cryptococcus



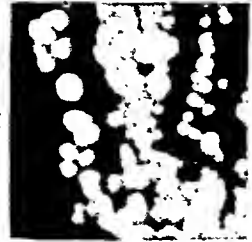
1



2



3



4A



1B



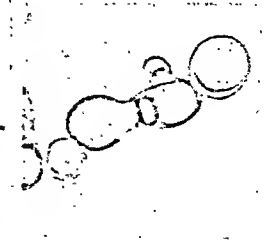
2A



3A



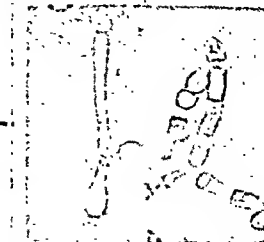
4B



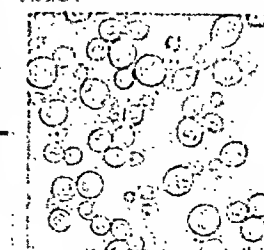
1C



2B



3B



4C

PLATE XI

STREPTOMYCIN AND LIPOTROPHIC AGENTS IN MILIARY TUBERCULOSIS

ALFRED C. GODWARD, Jr.¹

Miliary tuberculosis is generally considered by the medical profession as a fatal disease.

Since the introduction of streptomycin by Waksman, Schatz and Bugie (1) in 1944, the concept of therapy and the prognosis of the tuberculosis patient have somewhat changed, as indicated by the reports by Hinshaw and Feldman (2) and Hinshaw, Feldman and Pfuetze (3). In the latter paper, 12 patients with generalized hematogenous tuberculosis are included; 6 of the 12 were still living (all but one had tuberculous meningitis) though each showed clinical signs of residual infection.

There have been a few reports of patients with miliary tuberculosis recovering spontaneously. However, laboratory proof of the infection and clinical details of such cases are not always complete.

We present a patient with miliary tuberculosis, proved by bacteriological and laboratory identification, treated with streptomycin and lipotrophic agents at the U. S. Naval Hospital, Oakland, California, in whom a complete clinical recovery appears to have resulted.

CASE REPORT

R. B., a 19-year-old Marine, private first class, was admitted to the sick-list in Hawaii in July, 1945, at which time he complained of malaise, headache, chilliness and generalized aching. His temperature was 102.6° F. Physical examination revealed splinting of the left side of his chest on inspiration. An X-ray film showed an effusion in the left pleural space. He was treated with bed-rest and thoracentesis, and then evacuated to the United States, arriving at U. S. Naval Hospital, Oakland, on October 4, 1945.

At the time of arrival the patient was asymptomatic with the exception of mild dyspnea on exertion. Physical examination revealed dullness over the left lower chest. Laboratory tests were normal with the exception of a sedimentation rate of 20 mm. (Westergren) in one hour. Chest roentgenogram revealed a residual pleural effusion on the left side. He was treated with bed-rest and symptomatically. The sedimentation rate gradually returned to normal and the chest, according to further X-ray pictures, showed gradual clearing.

In the latter part of November the patient was sent home on a convalescent leave of two months' duration. Upon returning to the hospital on January 20, 1946, he stated that he had felt well throughout his leave. During the latter part of the leave he was employed as a taxi driver, which required long hours of daily work. A chest film at this time showed further clearing of the residual effusion and all laboratory data were normal.

Preparations were made to return the patient to duty when, on February 3, 1946, he complained of severe stabbing pains in the left chest and he had a chill. The following day his temperature rose to 102° F. and he had a second chill, bed-shaking in character.

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A chest roentgenogram was taken and typical snowstorm-like densities were seen throughout both lung fields (figure 1).

Mantoux skin tests with OT up to 1 mg. and PPD up to 0.05 mg. were negative. The sedimentation rate was 3 mm. (Westergren) in one hour. The blood count was normal.

The patient's course became progressively more stormy. Temperature, pulse rate and respiration gradually increased. He became more toxemic and uncoöperative. In the latter part of February, pleural effusion developed on the right side. Fluid withdrawn from this effusion was straw colored. The differential cell count revealed 98 per cent lymphocytes and the fluid readily formed a pellicle. A guinea pig injected with this fluid died in twenty-eight days. Autopsy of this guinea pig showed disseminated tuberculosis. Tubercle bacilli were seen in large numbers throughout all the tissues.

A urine specimen injected into a second guinea pig resulted in its death in thirty-two days and the autopsy showed generalized tuberculosis.

The patient was treated symptomatically and he received repeated blood transfusions. However, his condition became worse. Nausea and vomiting occurred after each attempted feeding. Diarrhea (eight to ten stools a day) became persistent. Changes in the sensorium became evident. The patient would cry when he was touched or when his bed-clothes were moved. On March 1, 1946, a tubercle was seen in the right retinal field approximately at the eleven o'clock position. The patient had a stiff neck on antero-flexion. No other signs of meningeal involvement were evident. Spinal puncture was done at this time and revealed that the pressure, cell count and chemistry were normal. Culture of the spinal fluid for acid-fast bacilli and guinea pig inoculation were not done.

Streptomycin therapy was started March 15, 1946, approximately six weeks after recognition of the disease, at which time the condition of the patient appeared to be terminal. His weight had dropped from 145 to 112 pounds. He had become cyanotic and required continuous oxygen inhalation. His temperature rose to 105° F. daily. His liver was palpable three finger breadths below the right costal margin. The spleen was not palpable. Pitting edema of the extremities was present and an enlarged heart with pulmonary congestion (figure 2) became manifest.

Total plasma proteins were 6.1 g. with 2.4 g. albumin and 3.7 g. globulin. The cephalin-cholesterol test was 3-plus; the urine urobilinogen was positive through a dilution of 1:640. The electrocardiogram showed flattening of the T waves in lead I, and notched QRS complexes and elevated ST segments in lead C F 4. Interpretation was that of nonlocalized toxemia of the myocardium. The blood was essentially normal and the sedimentation rate remained unaccelerated. Prothrombin time was 72 per cent of normal. Determination of calcium, phosphorous and phosphatase content of the blood and the platelet count, bleeding and coagulation time were normal.

The patient received 0.2 g. (200,000 units) of streptomycin intramuscularly every three hours, or 1.6 g. daily. In addition, he was given 5 g. of lipotropic agents (3 g. methionine, 2 g. choline chloride) a day. The methionine was given in the form of Amigen (containing 3 per cent methionine) of which he received 100 g. a day. The Amigen was given intravenously in the early phase of therapy and orally after foods were tolerated. The choline was given orally. This treatment was given for six months, during which time he received approximately 295 g. of streptomycin and 650 g. of the lipotropic agents. Streptomycin blood levels were not determined due to lack of equipment. The lipotropic agents were reduced from 5 g. daily to 3 g. daily after the second month (table 1). No toxic reactions were encountered during the course of therapy.

Three days after starting the above therapy, the patient's condition improved. Nausea and vomiting ceased as did the diarrhea. His appetite returned. Emotional instability

disappeared. The chest roentgenogram began to clear after three weeks. Five weeks after therapy, the white blood count rose to 16,300 with an actual increase in the neutrophil leucocytes. The sedimentation rate rose to 28 mm. per hour (table 1).

The tubercle in the right fundus disappeared in six weeks after the start of therapy. The temperature, pulse rate and respiration slowly took a downward course with considerable physical relief to the patient. Electrocardiograms became normal after seven weeks. The plasma proteins first showed an increase of globulin and finally of albumin with a normal albumin-globulin ratio. Liver function tests became normal. Plasma proteins and liver function tests required three and a half months to return to normal levels. Abnormal liver function tests, as well as the changes in the electrocardiogram, can be interpreted as due to the presence of tubercles in the liver and the myocardium or to a generalized toxemic condition, impairing hepatic and myocardial functions. The chest film became completely clear approximately four months after beginning of therapy (figure 3).

After six months the temperature remained normal and stable. With the increase in appetite, the patient gained weight up to 165 pounds, 20 pounds over his normal weight on October 1. Guinea pigs inoculated with urine specimens, two, four and six months after start of therapy, did not show evidence of tuberculosis on autopsy. Mantoux skin tests applied six months after therapy were positive to 0.01 mg. of OT. Twelve sputa and 6 gastric washings were negative on smear, and 3 gastric washings were negative on guinea pig inoculation throughout the course of observation.

The patient was allowed to become gradually ambulatory during the eighth month. At the present time he is completely ambulatory. He presents no symptoms of active disease and all laboratory data are normal. The patient is soon to be discharged from the Hospital and will be followed in the out-patient department.

DISCUSSION

The apparent recovery of this patient can most likely be attributed to the effect of streptomycin.

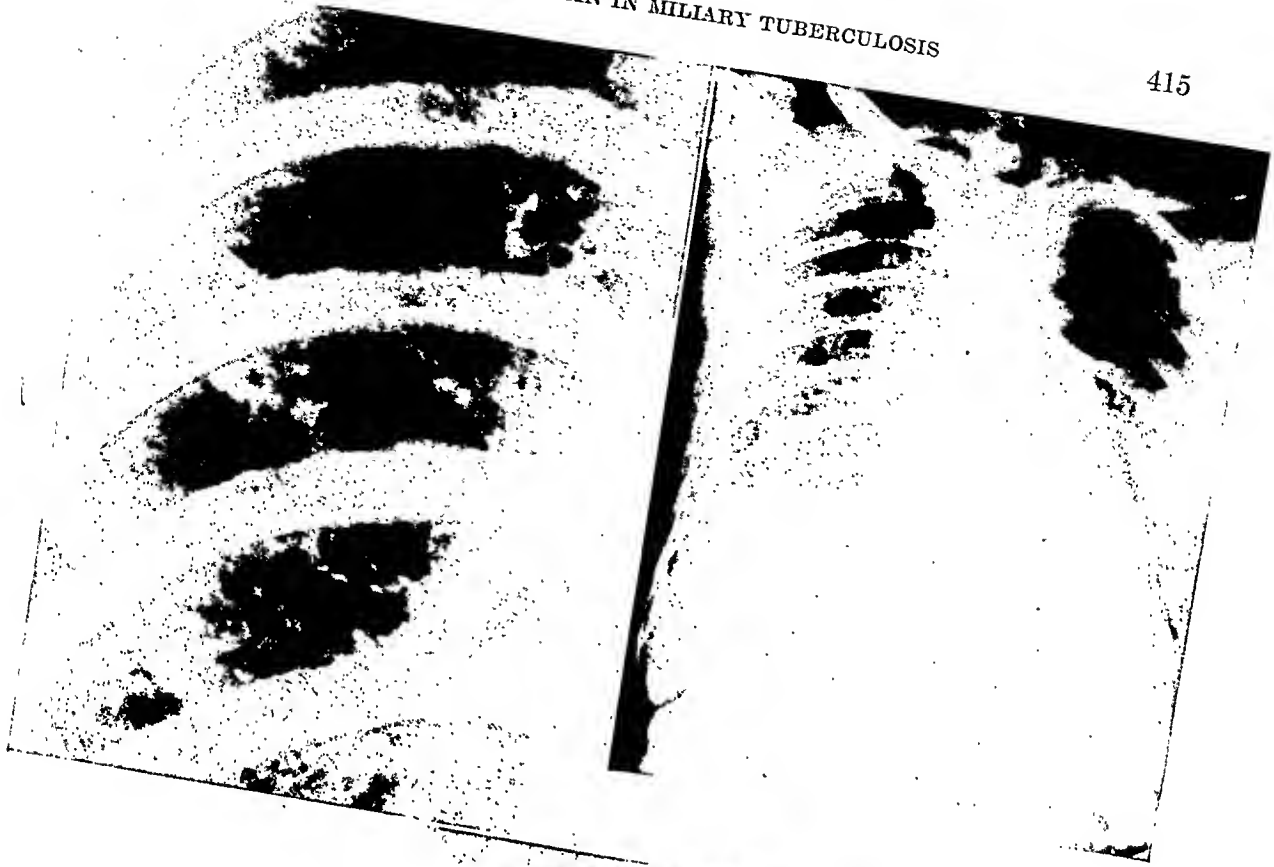
The diagnosis of miliary tuberculosis was proved by recovering tubercle bacilli from the pleural fluid and the urine, and by the observation of a tubercle in the right retinal field. Twelve sputa and 6 gastric washings were negative on smear, and 3 gastric washings were negative on guinea pig inoculation. The inability to recover tubercle bacilli from the bronchial secretions was most probably due to the acuity of the hematogenous lesions and the brief duration of the disease which was probably not long enough for intrabronchial spread or rupture of pulmonary lesions into the bronchial tree.

The question as to whether this patient's disease was primary tuberculosis

FIG. 1. (Upper left) Partial roentgenogram of chest, taken February 5, 1946, demonstrates miliary disseminated shadows, interpreted as miliary tuberculosis. A typical area is shown for demonstration of roentgenographic details.

FIG. 2. (Upper right) Roentgenogram of heart and chest, taken March 9, 1946, six days before starting streptomycin, showing enlarged heart and generalized spread of tuberculous process with an area of pneumonic consolidation in the left mid-lung field.

FIG. 3. (Lower) Film taken July 1, 1946, showing normal lung fields, three and one-half months after beginning treatment with streptomycin and lipotropic agents. (Same area as shown in figure 1.)



Figs. 1-3

TABLE 1
Clinical, laboratory and therapeutic data
Averages of these data by months

	103.8	100.5	99.3	98.7	98.7	98.6	98.6	98.6
Temperature, F.	103.8	100.5	99.3	98.7	98.7	98.6	98.6	98.6
Pulse rate	132	116	110	100	80	76	72	72
Respiratory rate	36	27	23	20	19	18	18	18
White count	6,300	9,600	16,300	7,400	7,300	7,600	6,800	7,100
Sedimentation rate (Wester-gren) in mm. per hour	9	17	28	14	16	12	9	6
E.C.G. (interpretation).....	General toxemia	General toxemia	N*	N	N	N	N	N
Urine urobilinogen (highest dilution positive)	1:640	1:160	1:80	1:80	1:80	1:20	1:10	1:10
Plasma proteins (grams per 100 cc.)								
Total.....	6.1	7.8	8.5	7.9				
Albumin.....	2.4	3.0	4.5	5.2	N	N	N	N
Globulin.....	3.7	4.8	4.0	2.7				
Cephalin-cholesterol.....	3	2	1	N	N	N	N	N
Prothrombin time, per cent of normal.....	72	78	100	100	100	100	100	100
Vital capacity (normal = 4.6 lt.)					2.2	2.8	3.2	4.0
Weight in pounds (average weight before illness 145 pounds).....	112	121	130	143	149	154	160	165
Treatment (in g. per day)								
Streptomycin.....	1.6	1.6	1.6	1.6	1.6	1.6	0	0
Methionine.....	3	3	3	3	3	3	0	0
Choline chloride...	2	2	0	0	0	0	0	0
Month.....	March	April	May	June	July	August	September	October

* N = normal.

or reinfection tuberculosis cannot be stated with certainty. The history of a tuberculous pleural effusion seven months before the onset of his hematogenous dissemination would favor the belief that the seeding occurred from localized chronic foci and that the miliary spread occurred during the reinfection phase.

The importance of the lipotrophic agents in the treatment of this case is not known. It is possible that a recovery would have resulted with the use of streptomycin alone. Hinshaw, Feldman and Pfuetze (3) report a patient with miliary tuberculosis recently started on streptomycin who still is in remission.

Lipotropic agents were used because of the observation that they appeared to cause quiescent tuberculous infections not treated with streptomycin to exacerbate. It could be postulated that such agents have an effect on the lipid substance of the bacillus or the fatty caseous material of the tubercle, altering the permeability or tissue environment, so as to allow the bacillus to multiply more rapidly when not checked, and rendering the patient more vulnerable to the action of specific antibiotics. Further investigation of the combination of streptomycin and lipotropic agents in the treatment of tuberculosis appears warranted.

SUMMARY

A case of proved miliary tuberculosis was treated with streptomycin and lipotropic agents with apparent complete recovery of the patient.

SUMARIO

La Estreptomicina y los Agentes Lipotrofos en la Granulía

Un caso de granulía comprobada fué tratado con estreptomicina y agentes lipotrofos, obteniéndose aparentemente la curación total del enfermo.

Acknowledgments

Sincere appreciation is given to Admiral A. H. Dearing, M.C., U. S. N., Officer in Command of U. S. Naval Hospital, Oakland, California, and Captain E. F. Evans, M.C., U. S. N., Chief of Medical Service, U. S. Naval Hospital, Oakland, California, whose insight and complete coöperation made the treatment of this case possible.

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STREPTOMYCIN IN RESECTION IN PULMONARY TUBERCULOSIS

Report of Five Cases

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In 1944, Schatz, Bugic and Waksman (5) isolated streptomycin from cultures of a group of actinomycetes of the soil—*Streptomyces griseus*. During the ensuing two years Feldman and Hinshaw (1, 2, 3, 4), who made a series of well-controlled clinical and experimental studies, demonstrated conclusively the suppressive and inhibitory effect of streptomycin on the tubercle bacillus.

Streptomycin may well be effective in exerting its stabilizing influence in the preoperative and postoperative period in patients with pulmonary tuberculosis, in whom surgical intervention is done, in order to prevent the spread of the tuberculous process or to protect areas newly exposed as the result of trauma and manipulation.

The following case reports indicate what may be accomplished in the future. The plan of attack falls far short of the desired goal and was dictated by the limited supply and impure state of certain early lots of streptomycin. The impurities now have been largely eliminated and the increasing availability of supplies undoubtedly will provide the necessary amount of the drug for more extensive investigation than has been possible to date.

CASE REPORTS

Case 1: An unmarried white woman, 32 years of age, registered at the Mayo Clinic on September 15, 1945. She had been in poor health for ten years. Her illness began with an episode of fever, productive cough and night sweats in 1935. At that time an inflamed lymph node in the right cervical region was incised and the wound was drained. In 1938 examinations of the sputum were thought to reveal the presence of tubercle bacilli. By 1939 her cough was productive of small amounts of blood and in 1940 she suffered a severe pulmonary hemorrhage. In 1941 bronchoscopy was performed and an ulcer was cauterized. Her general health improved, although roentgenograms of the thorax at that time revealed an obstructing lesion in the right upper lobe bronchus. In 1942 wheezing developed and was present at the time of her examination at the Clinic. No further roentgenograms of the thorax were taken until early in 1945 when she experienced an attack of "grippe" with cough, hemoptysis and fever. She was told that the roentgenogram taken at that time revealed the presence of a pulmonary tumor.

On physical examination on her admission here the patient was a normal-looking young woman in apparent good health. No abnormalities other than those in the thorax were found. Laboratory studies revealed hemoglobin, 12.5 g.; erythrocyte count, 3,450,000; leucocyte count, 7,400; and sedimentation rate, 21 mm. per hour (Westergren method). Results of urinalysis were negative. The roentgenologist reported that fibrous and calcified tuberculosis involved the upper lobe of the right lung. A poorly defined mass was

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noted in the region of the hilum of the right lung (figure 1a). Repeated examinations of the sputum showed large numbers of tubercle bacilli.

On bronchoscopic examination considerable scarring on the right lateral and inferior walls of the right main bronchus was observed immediately above the orifice of the right upper lobe bronchus. The scarring produced slight narrowing of the right main bronchus. No ulceration was present. The scars probably resulted from previous cauterization with silver nitrate. The diameter of the orifice of the upper lobe was reduced to 2 mm. A small tongue of granulation tissue protruded from this orifice and a moderate amount of secretion appeared to be coming from the lobe.

The patient was hospitalized and daily intramuscular administration of 120,000 units of penicillin was begun on September 22. On September 26 the middle and upper lobes of the right lung were removed and the phrenic nerve was crushed. Bronchoscopy was performed before the patient was returned to her room. The pathologist reported that diffuse caseous tuberculosis was present in the middle and upper lobes. A tuberculous abscess, 6 cm. in diameter, was present in the upper lobe. Lymph nodes showed caseous tuberculosis. Her postoperative clinical course was satisfactory, and the wound healed by primary intention. Tubercle bacilli, however, were found repeatedly in her sputum. The source of these bacilli caused considerable concern. Postoperatively, bronchoscopy was performed and 0.5 g. of streptomycin was insufflated into the bronchial tree. No ulcerations were seen and the bronchial stump looked clean. Bronchoscopy was repeated on two subsequent occasions, but a pathological condition was not found. Nebulization with a solution containing 200,000 units of penicillin and 0.5 g. of streptomycin was begun on October 1. This treatment was given until October 13 and was repeated from November 7 to 26. In addition, 1.0 g. of streptomycin was administered intramuscularly daily from October 13 to November 15. Occasional examination of sputum still gave positive results. On November 16, in addition to nebulized streptomycin, the dose of streptomycin which was being given intramuscularly was doubled to 2.0 g. daily and this dose was given until December 12 when toxemic reaction to streptomycin became apparent. This reaction consisted of dizziness, blurring of vision and vertigo. For an additional week, after administration of streptomycin was stopped, 120,000 units of penicillin were administered intramuscularly each day. Beginning on December 15 examination of sputum for tubercle bacilli was carried out daily for eleven days and results were all negative. Cultures of gastric content obtained on December 20 were negative. About sixty days later material obtained by gastric aspiration was used for guinea pig inoculations twice and no evidence of tuberculosis was found. Cultures of the same material were negative.

On December 27, when the patient was dismissed from the Clinic, she was in good condition (figure 1b), save for residual dizziness, blurring of vision and slight unsteadiness. At last report on April 1, 1946, all evidence of toxemia had disappeared, her cough had cleared and her health seemed excellent although her temperature occasionally rose to 99° F. in the evening.

Case 2: A married white woman, 44 years of age, registered at the Mayo Clinic on April 20, 1946. She was known to have had pulmonary tuberculosis for five years. In 1941 the Mantoux test gave positive results and a roentgenogram of the thorax revealed a lesion of questionable activity. In 1943 cough developed and a roentgenogram of the thorax showed tuberculous involvement in the hilar region of the left lung. Although the patient remained at rest in bed, the tuberculous lesion spread. At bronchoscopic examination in 1944, an area of reddening in the main bronchus of the left lung was observed. Treatment consisted of crushing the left phrenic nerve and keeping the patient at rest in bed. One



FIG. 1. (Case 1) (Upper left) *a*: Cavitation and fibrosis in right upper lobe and residual lipiodol in right lower lobe before operation; (Upper right) *b*: complete re-expansion of the lower lobe about two months after operation.

FIG. 2. (Case 2) (Lower left) *a*: Marked bronchial stenosis with suppuration and cavitation distal to obstruction, considerable shift of mediastinal structures to the left and small area of infiltration anteriorly in the third interspace on the right at time of admission; (Lower right) *b*: clearing of left upper lobe after a period of treatment with streptomycin before operation.

STREPTOMYCIN

year later, bronchoscopy was repeated and the findings were essentially the same as those reported previously. Diasone and penicillin produced temporary improvement. In the fall of 1945, cough recurred and she was given treatment with nebulized promin daily for five months. In the spring of 1946, bronchoscopy indicated improvement in the bronchial lesion but according to the roentgenogram there appeared to be a spread in the lower lobe of the left lung.

On admission to the Clinic the patient looked well, although she did have a slight cough, low-grade fever and signs of atelectasis of the left lung. Laboratory studies revealed that the urine was normal; hemoglobin was 13.0 g.; erythrocytes numbered 4,400,000 and leucocytes, 14,000; and sedimentation rate was 95 mm. per hour (Westergren method). Repeated examination of the sputum gave positive results. The roentgenogram of the thorax revealed a chronic diffuse inflammatory process involving the entire left lung. Multiple small cavities were noted in the left lung. There was a small area of involvement in the right anterior third interspace, marked pleural thickening and retraction of the mediastinum to the left and compensatory emphysema in the right lung (figure 2a). On bronchoscopy, on April 23, the trachea and right bronchial tree appeared to be normal but the mucous membrane was pale. There was marked stenosis of the left main bronchus 3 cm. from the coryna. The stenosed orifice which was elliptical measured 3 by 6 mm. No ulceration was noted. Thick glairy secretions obtained from the region of the stenosis contained tubercle bacilli.

On April 25, daily intramuscular administration of 1.5 g. of streptomycin was begun (figure 2b). In addition, on April 30, daily nebulization with 0.5 g. of streptomycin was started. The patient noted light-headedness and some blurred vision on May 12 but true vertigo was not present. Nebulization was stopped but parenteral administration was continued. By May 23, dizziness had become more severe; she vomited occasionally and some nystagmus occurred when she was in a sitting position. Administration of streptomycin was discontinued. By this time no acid-fast bacilli were found when the sputum was examined. Bronchoscopy, on May 28, showed essentially the same condition as was found the last time it was performed and tubercle bacilli were found in aspirated secretions.

On June 5, intramuscular administration of streptomycin was started again in the same dosage and daily intramuscular administration of 160,000 units of penicillin was begun. The next day left pneumonectomy was performed. The left phrenic nerve was interrupted permanently and the pleural cavity was closed without drainage. Bronchoscopy was performed before the patient was taken to her room. The pathological report stated that tuberculosis of the lower lobe of the left lung and hilar lymph nodes was extensive and that the left main bronchus was stenosed. The upper lobe of the left lung apparently had not been involved in the tuberculous process, but at the time of admission was the seat of retained secretions (figure 2a) which apparently drained after a period of treatment with nebulized streptomycin (figure 2b), thus allowing the mediastinum to return to a more normal position.

The patient's postoperative clinical course was uneventful. Results of examination of the sputum were positive on June 10 and 12 but subsequently many examinations were made and results were all negative. The dose of streptomycin was increased to 3.0 g. on June 13. One week later administration of all drugs was stopped. When a specimen of fluid obtained from the left pleural cavity on June 25 was used for guinea pig inoculation evidence of tuberculosis was not found. When gastric material was used for the same study on July 2 results were again negative. The toxic symptoms had decreased in severity but were still present.

The patient was dismissed and returned to a sanatorium early in July, 1946, and at last report, on August 26, her temperature had remained normal. She had no cough and only slight dizziness was present at times. Roentgenograms revealed that the lesion in the right lung had remained stationary and the presence of fluid in the left portion of the thorax had not caused mediastinal shift. Although she was still at rest in bed she was about to begin a program of exercise.

Case 3: A white married woman, aged 34, registered at the Mayo Clinic on May 12, 1946. She was known to have had pulmonary tuberculosis since March, 1935. At that time she had had a cough; results of examination of the sputum were positive, and roentgenological evidence of cavitation in the lower lobe of the right lung was found. Permanent interruption of the right phrenic nerve was carried out and the patient remained at rest in bed for six months and then she returned to work. She was married in 1938. In 1940 cough recurred, sputum from a cavity in the upper lobe of the left lung contained tubercle bacilli. Artificial pneumothorax on the left combined with a short period of rest in bed kept her symptom-free until July, 1943, when hemoptysis occurred suddenly. A roentgenogram revealed a fresh cavity in the upper lobe of the right lung and a well-controlled pneumothorax on the left. Artificial pneumothorax was instituted on the right side and her condition improved.

In June, 1944, the cavity on the right reopened and symptoms recurred. There followed two years of variable health. The cavity seemed to close and sputum became negative but then the cavity would reopen. Pneumoperitoneum provided some temporary benefit. Bronchoscopy in December, 1945 revealed no bronchial lesion but secretions from the right lung contained tubercle bacilli. After March, 1946, the left pneumothorax was not maintained.

When the patient was examined at the Clinic her condition presented a most difficult problem. The upper lobe of the right lung in which pneumothorax was being maintained contained an open cavity, each day she raised one ounce of sputum which contained tubercle bacilli and she had a low-grade fever, wheezing on exertion and obliterative pleuritis on the left. Some evidence of a long-standing small cavity was found in the upper lobe of the left lung under pneumothorax (figure 3a). She insisted that pulmonary resection be performed regardless of the outcome.

Laboratory studies revealed that the urine was normal; hemoglobin, 13.1 g.; erythrocyte count, 4,190,000; leucocyte count, 9,500; sedimentation rate, 25 mm. per hour (Westergren method); serum protein, 6.9 g.; the albumin-globulin ratio was normal. Daily examination of sputum gave positive results.

On May 15, bronchoscopy was performed but no evidence of a bronchial lesion was seen. Some purulent secretions were coming from the orifice of the upper lobe of the right lung and the mucosa in this region was somewhat red. It was thought that bronchial disease was present in the upper lobe of the right lung but evidence of it could not be seen.

Due to the lack of streptomycin the patient at first was given 200,000 units of penicillin daily by nebulization. This treatment was begun on May 18. In addition, 160,000 units were given intramuscularly. On May 31, the intramuscular administration of penicillin was stopped and a total of 2.0 g. of streptomycin was given intramuscularly day and night. The daily dose was divided and given every three hours.

Despite the unfavorable conditions, on June 4 the upper lobe of the right lung was removed through a posterolateral incision. This type of incision was used in all of the 5 cases herein reported. The phrenic nerve was crushed after lobectomy, and bronchoscopy for the removal of secretions was performed immediately afterward, as is routine at the

Clinic. The pathological report stated that extensive caseous tuberculosis was present and a cavity, 4 cm. in diameter, was present in the lobe.

The patient's postoperative condition was satisfactory despite the difficulty of reexpanding the lower lobe of the right lung (figure 3b). Daily postoperative examinations of sputum revealed no tubercle bacilli. A specimen of pleural fluid obtained on June 13 was inoculated into two guinea pigs but no evidence of tuberculosis was found. Administration of streptomycin and penicillin was discontinued on June 17 because of lack of supply. No toxic reactions to streptomycin were noted. Examination of gastric contents on July 1 did not reveal acid-fast bacilli.

When the patient was dismissed on July 1 no evidence of spread to either pulmonary field was found. The operative wound was healed completely. She continued to rest in a sanatorium and follow-up reports on July 15 and August 11 stated that the sputum did not contain tubercle bacilli, that evidence of spread of tuberculosis was not found in roentgenograms and that the patient was gradually beginning to exercise.

Case 4: On June 1, 1946, a white man, 44 years old, reregistered at the Mayo Clinic. When he was a patient at the Clinic in 1935 he had undergone bilateral lumbar sympathectomy for Buerger's disease. In 1945 he underwent cholecystectomy for cholecystitis with cholelithiasis.

The history of pulmonary tuberculosis dated from about February, 1942, when he was admitted to a sanatorium. At that time there was a cavity in the upper lobe of the right lung, the patient had a cough and sputum contained tubercle bacilli. During the ensuing nine months pneumothorax with closed pneumonolysis was ineffective in closing the cavity. A two-stage posterior thoracoplasty with removal of seven ribs resulted in spread of the disease into the lower lobe. Although the patient remained at rest in bed for the next year no change in his condition was noted. The right phrenic nerve was crushed in January, 1944, but this operation did not aid in closing the cavity and his sputum continued to contain tubercle bacilli. Early in 1945, complete posterior revision operation and anterior thoracoplasty in stages again failed to close the cavity. Although the patient's general condition remained remarkably good he was kept in the sanatorium for four years because of cough and presence of tubercle bacilli in the sputum.

On admission at the Clinic the patient had been moderately active for six months and respiratory reserve seemed good, but each day he was raising more than an ounce of sputum which contained tubercle bacilli.

The urine was normal; hemoglobin, 13.9 g.; erythrocyte count, 4,900,000; leucocyte count, 17,000; and sedimentation rate, 48 mm. per hour. Tubercle bacilli were found in the sputum at every examination.

Roentgenograms of the thorax indicated that thoracoplastic procedures had been performed on the right side with some regeneration of the ribs. A lesion with cavitation was present in the upper lobe of the right lung. Bronchoscopic examination showed evidence of chronic bilateral bronchitis which was more marked on the right side. Mucopurulent secretions came from the upper lobe of the right lung and the mucosa of the right upper lobe bronchus was inflamed and mildly edematous. No evidence of ulceration or stenosis was noted.

On June 4, 1.5 g. of streptomycin was administered intramuscularly and this treatment was continued daily. A week later, daily administration of 160,000 units of penicillin was added. The same day right pneumonectomy was performed by one of us (O. T. C.). The right phrenic nerve was interrupted and postoperatively bronchial secretions were thoroughly aspirated bronchoscopically. His postoperative course was without incident.

Pathological examination of the lung revealed a tuberculous cavity, 3 by 2 by 2 cm., in the upper lobe and caseous involvement of the hilar lymph nodes. In the middle and lower lobes there was extensive fibrosis but no active tuberculous foci such as were suspected preoperatively. On June 19, administration of streptomycin was discontinued because high-pitched tinnitus occurred. This cleared up shortly and the patient returned to the sanatorium on June 26. Last report, on August 2, stated that roentgenograms showed that the left lung had remained clear, temperature, pulse and respirations were normal, all signs of tinnitus had disappeared and the patient had been ambulatory for more than two weeks and was about to be dismissed from the sanatorium.

Case 5: An unmarried white woman, 29 years of age, registered at the Mayo Clinic on June 10, 1946. Although questionable roentgenological evidence of a pulmonary tuberculous lesion had been found in 1938 during a period when the patient was run-down, no treatment other than rest was advised and subsequent roentgenograms (the last in 1943) revealed no abnormalities. In July, 1945, when the patient was hospitalized because of a persistent hacking cough, roentgenological examination revealed a pneumonic shadow in the right lung. Examination of the sputum showed tubercle bacilli. She was sent to a sanatorium where pneumothorax was instituted in September. Apparently a good collapse was obtained, no adhesions were present and by February, 1946 the patient insisted on going home where she continued to rest in bed. In April, 1946 wheezing developed, cough increased, temperature became elevated and roentgenological examination revealed extensive cavitation under the pneumothorax.

On admission of the patient at the Clinic two months later she looked remarkably well although pale. She had a cough and was experiencing some chills and night sweats. Urine was normal; hemoglobin, 13.5 g.; erythrocyte count, 4,300,000; leucocyte count, 3,700; blood urea, 24 mg.; and sedimentation rate, 113 mm. per hour. Results of daily examination of sputum for tubercle bacilli were strongly positive. Roentgenograms of the thorax showed partial right pneumothorax, apical pleural adhesions, moderate effusion and extensive sacular cavitation of the entire upper lobe of the right lung and probable involvement of the middle lobe and atelectasis of the lower lobe (figure 4). Bronchoscopic examination on June 13 showed definite narrowing of the right main bronchus with stenosis of the right upper lobe bronchus.

No streptomycin was available. Because the patient had a spiking temperature curve which daily rose to 101° F. and lesions of the so-called hot type, intramuscular administration of penicillin was started and 120,000 units were given daily. Right pneumonectomy was necessary and after consideration of the risks involved it was decided that the right lung should be removed "now or never."

FIG. 3. (Case 3) (Upper left) *a*: Bilateral pneumothorax with a large cavity in the right upper lobe and questionable small cavity in the left upper lobe with a small amount of fluid in the left pleural space; (Upper right) *b*: incomplete reexpansion of right middle and lower lobes after right upper lobectomy. Recent roentgenogram has shown practically complete expansion of the remaining portion of the right lung obviating possible thoracoplasty.

FIG. 4. (Case 5) (Centre) Preoperative pneumothorax on the right, marked stricture of the right main bronchus and distal suppuration and cavitation.

FIG. 5. (Case 5) (Lower left) *a*: Seventeen days after pneumonectomy; right pleural space half filled with fluid; tuberculous spread anteriorly into the left third and fourth intercostal spaces; (Lower right) *b*: five weeks after *a*, no further progression on the left side during treatment with streptomycin. The apparent difference is due to changes in roentgenological technique.

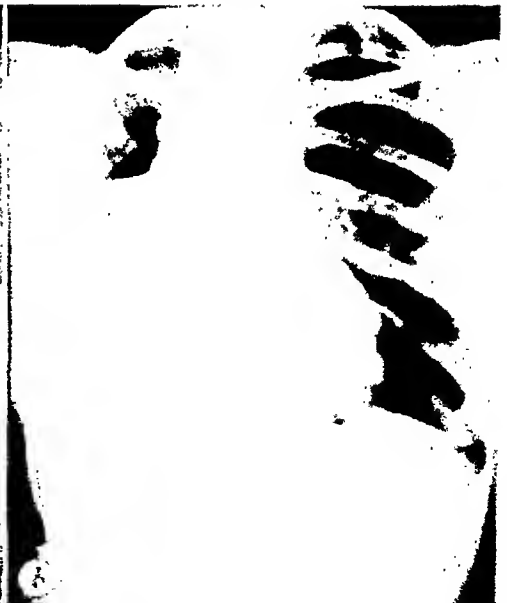
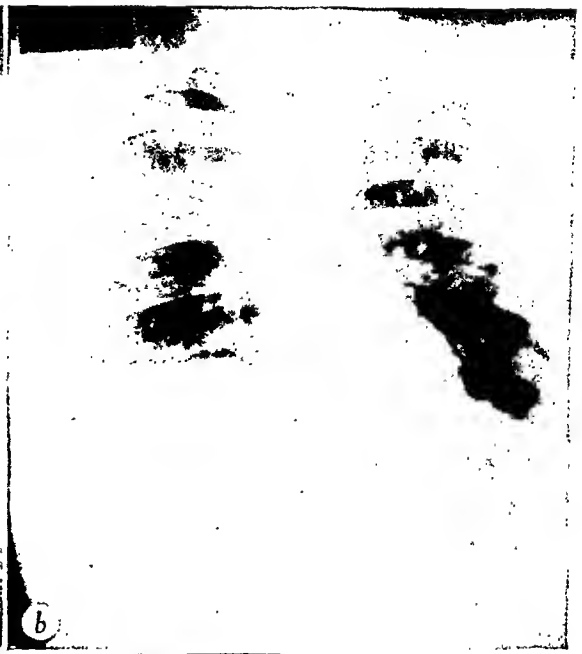


FIG. 3-5

tomy was performed on June 25. The right phrenic nerve was interrupted and postoperative bronchoscopy was carried out. The operative specimen showed caseous tuberculosis involving the entire lung, tuberculous and pyogenic abscesses and caseous and inflammatory involvement of all hilar nodes. The bronchial involvement extended into the right lower lobe bronchus which resulted in atelectasis. The postoperative reaction was immediate and intense with high temperature and pulse rate. Roentgenogram of the thorax on June 27 revealed an area of infiltration in the upper lobe of the left lung and the question arose as to whether this was evidence of tuberculous spread or of retained secretions and resultant nonaeration (figure 5a). Bronchoscopy was performed and a moderate amount of thick mucoid secretion was seen in the trachea, left main and upper lobe bronchi. This was aspirated and sent to the laboratory for culture and 1.0 g. of streptomycin was instilled into the left bronchial tree. No tubercle bacilli were found in the specimen.

A daily dose of 2.4 g. of streptomycin was then combined with the dose of penicillin. The patient recovered satisfactorily but spiking of the temperature curve recurred after eight days. The pleural space on the right was tapped on four occasions during the next week, small amounts of serosanguineous fluid were withdrawn and 100,000 units of penicillin and 0.1 g. of streptomycin were instilled. Empyema did not develop and the pleural fluid was found to be free of acid-fast bacilli. Temperature, pulse and respirations became normal two weeks later and remained so thereafter. The daily dose of streptomycin was reduced to 1.6 g. on August 5, and the administration of penicillin was discontinued. Slight vestibular symptoms occurred eighteen days after the administration of streptomycin was begun but subsided entirely although administration of streptomycin was not stopped. Our plan at the time of this writing is to continue to give streptomycin for several more weeks. Hence this treatment will have been given for three full months postoperatively. Sedimentation rate has dropped to 5S mm. in one hour and repeated roentgenographic examination has revealed no advance in the original contralateral spread (figure 5b).

COMMENT

It must be stated clearly that the therapeutic success in these cases is not presented in the sense of a *fait accompli*. Without question, the course in many cases parallels the course in these in which streptomycin has been used. We do think, however, that the results in these 5 consecutive cases are sufficiently encouraging to warrant the continued trial of combined surgical and antibiotic treatment. Although streptomycin will shortly be available in increasing amounts, it will be many months before supply can begin to approach demand. Under these conditions, it is suggested that, whereas treatment of established disease may require vast quantities of the drug, prevention may require considerably less and that in this prophylactic sense streptomycin may find its greatest field of service.

SUMMARY

A series of 5 case reports is presented to suggest the possibilities of combining treatment with streptomycin with radical surgical procedures in some highly selected types of pulmonary tuberculosis. While the series is not sufficient to indicate clearly that any prophylactic or therapeutic effect was realized, it is

intended to indicate the possibility of utilizing the suppressive effect of streptomycin during the crucial period before, during and after radical surgery.

It is believed that, should streptomycin be successful in preventing bronchogenic and hematogenous extension of pulmonary tuberculosis during and after operation, or should it prevent development of such a complication as tuberculous empyema, it will reduce surgical mortality and broaden the indications for radical surgical treatment of pulmonary tuberculosis.

SUMARIO

La Estreptomicina en la Resección en la Tuberculosis Pulmonar

Preséntase esta serie de cinco historias clínicas con mira a indicar la posibilidad de combinar la estreptomicinoterapia con los procedimientos cruentos radicales en ciertos casos muy seleccionados de tuberculosis pulmonar. Aunque la serie no basta para indicar netamente que se obtuviera efecto profiláctico o terapéutico, sí indica la posibilidad de utilizar el efecto supresor de la estreptomicina durante el período crítico de la cirugía radical y antes y después del mismo.

Exprésase el parecer de que, de mostrar eficacia la estreptomicina para impedir la difusión broncogénica y hematogénica de la tuberculosis pulmonar durante la operación y después, o para impedir la aparición de una complicación tal como el empiema tuberculoso, reducirá la mortalidad quirúrgica y ampliará las indicaciones del tratamiento quirúrgico radical en la tuberculosis pulmonar.

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STREPTOMYCIN IN EXPERIMENTAL TUBERCULOSIS*

In Vivo Sensitivity to Streptomycin of Recently Isolated Strains of Human Tubercle Bacilli and Strains of Bovine Tubercle Bacilli

WILLIAM H. FELDMAN¹ AND H. CORWIN HINSHAW²

The original observations on the ability of streptomycin to exert a favorable influence *in vivo* on the course of experimental tuberculosis were made on infections established by the laboratory stock strain of tubercle bacilli known as H37Rv(1). Although this strain of tubercle bacilli has been maintained on synthetic medium for many years, relatively small doses of it still have a satisfactory virulence for guinea pigs. However, from a clinical point of view it seemed important to obtain information regarding the efficacy *in vivo* of streptomycin against previously uncultured strains of tubercle bacilli obtained directly from patients who had tuberculosis. Consequently a series of experiments were done utilizing as the infective agents several recently isolated human strains of tubercle bacilli, two bovine strains of tubercle bacilli and, for comparison, strain H37Rv.³

METHODS

The strains of tubercle bacilli used consisted of (1) seven primary isolation cultures, approximately 6 weeks old, of tubercle bacilli obtained from gastric aspirations of 7 patients who had severe, progressive, pulmonary tuberculosis; (2) two strains of bovine tubercle bacilli, one of which was the well-known Ravenel strain, the other bovine strain being isolated from a tuberculous lymph node of a bovine animal approximately fourteen months prior to use in the present experiment; (3) a subculture of H37Rv. With the exception of strain H37Rv, which was grown in the synthetic medium of Proskauer and Beck, described by us in a previous article (3), the respective strains were cultured on slants of egg-yolk medium.

One-tenth milligram of each strain of tubercle bacilli was used to inoculate subcutaneously ten groups each, consisting of 14 adult male guinea pigs. The animals were caged in pairs and fed the regular laboratory ration. Starting two weeks after the animals had been inoculated, 8 animals in each of the ten groups were treated daily with 6,000 micrograms of streptomycin. The drug was injected subcutaneously in four equal doses at six-hour intervals. Treatment continued for fifty-four days. The experiments were terminated sixty-eight days after the animals had been inoculated. At the time of necropsy, material representing the following tissues was preserved for subsequent microscopic study: axillary lymph nodes, subcutis at the site of inoculation, lungs, tracheo-bronchial lymph nodes, liver and spleen.

RESULTS

Comparative survival times: Of the 58 guinea pigs representing the untreated controls that lived two weeks or longer, 38 (66 per cent) died during the duration

* Streptomycin utilized in this study was supplied through the courtesy of Dr. D. F. Robertson, Merck and Company, Rahway, New Jersey.

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³ The results of these experiments have been referred to briefly in a previous publication (2).

of the experiment. A considerable number of the treated animals also died. Among 80 guinea pigs that received streptomycin, 28 (35 per cent) died. With the exception of one animal, the deaths of the untreated controls were presumed to be due to tuberculosis. The disease had disseminated widely and was present in amounts sufficient to have caused death.

In so far as signs of tuberculosis were concerned, the situation among the treated animals that died was in marked contrast to that recorded for the controls. With the exception of 4 animals that had received treatment for two days, three days, four days and eleven days, respectively, grossly visible parenchymal tuberculosis was not present at necropsy among the treated animals that died prematurely. The immediate cause of death of most of the treated animals that died was massive abdominal hemorrhage.⁴

Evidence of deterrent effects of streptomycin: The marked dissimilarity of the gross appearance of the untreated controls and the treated animals in the respective groups at the time of necropsy provided convincing evidence of the effect of the treatment. As may be noted in figures 1 to 5, proof of the pathogenicity of the respective strains of tubercle bacilli is conclusive. In most instances the disease in the control animals had involved the spleen, liver and lungs extensively with tuberculosis of the lymph nodes contiguous to the site of inoculation. The initial focus in the tissues of the suprasternal region had persisted and was progressive, with a few ulcerations commonly present. With few exceptions the disease in the untreated animals was typical of what would be expected in guinea pigs receiving subcutaneously a relatively large dose of fully virulent tubercle bacilli of the human or bovine type.

Very little tuberculosis was observed grossly in the animals in the respective groups that were treated for a minimum of fourteen days or longer. As a matter of fact, in 54 per cent of the 72 animals that received streptomycin for fourteen days or longer no lesions of tuberculosis were found either grossly or microscopically. The tuberculosis present in the remaining 46 per cent of the treated animals was for the most part minimal.

The results of the microscopic examination of the tissues obtained from untreated and treated animals in the ten groups are shown in figure 6. In this portion of the study an attempt was made to express numerically the units of tuberculosis in the various sites of predilection.⁵

An examination of the data indicates that streptomycin was equally effective in suppressing the infection produced by the seven recently isolated strains of human tubercle bacilli, the Ravenel strain of bovine tubercle bacilli and the laboratory stock strain H37Rv. The infections produced by the other bovine strain of tubercle bacilli appeared microscopically to be somewhat more resistant to the deterrent action of streptomycin than was true of the other nine strains.

⁴ It appears likely that the abdominal hemorrhage was the result of injudicious restraint of the animals to facilitate medication. After measures were taken to preclude such presumed accidents few additional instances of abdominal hemorrhage have been noted.

⁵ A suggested scheme for recording experimental tuberculous changes numerically has been described previously (4).

However, even in this instance the lesions present were microscopic in size and nonulcerating in character and did not reveal evidence of progression.

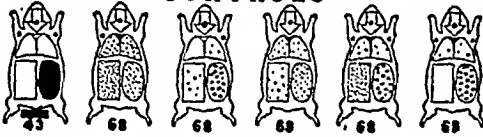
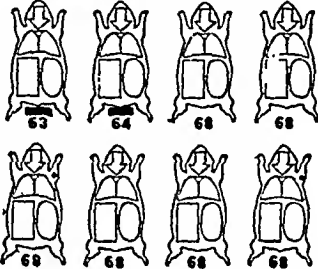
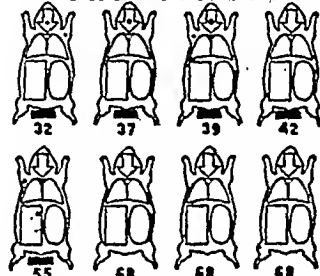
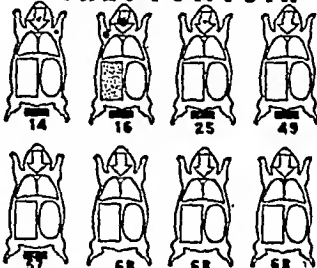
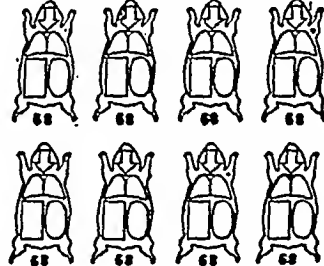
H37RV**CONTROLS****STREPTOMYCIN****HOMO NO. 2****CONTROLS****STREPTOMYCIN****HOMO NO. 1****CONTROLS****STREPTOMYCIN****HOMO NO. 3****CONTROLS****STREPTOMYCIN**

FIG. 1. (Left) Effects of streptomycin therapy in two experiments. The strains of tubercle bacilli used for inoculations were the stock strain H37Rv and an original isolation culture from a patient who had severe pulmonary tuberculosis. Guinea pigs dying before the termination of the experiment are indicated by black bars. The number under each animal in figures 1 to 5 indicates its survival time in days following infection.

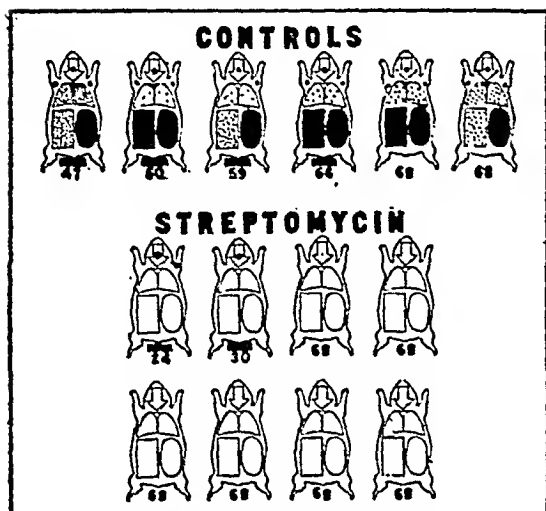
FIG. 2. (Right) Effects of streptomycin therapy in two experiments. The strains used for inoculations were original isolation cultures from patients who had severe pulmonary tuberculosis.

COMMENT

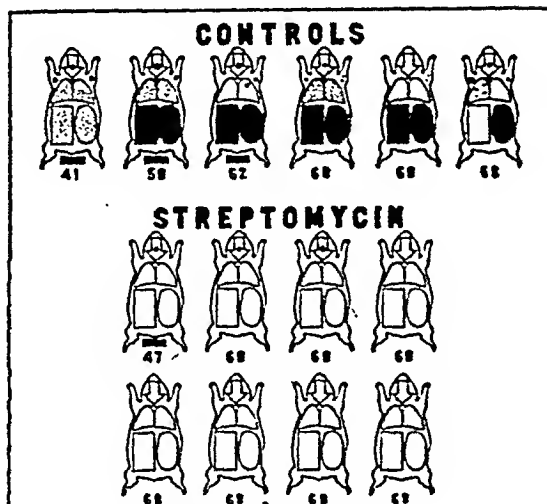
This study has yielded results quite consistent with the results of the earlier experiments *in vivo* with streptomycin. The ability of streptomycin to control

tuberculous infections in guinea pigs successfully is substantial and readily demonstrable. Although the experiments were of relatively short duration the

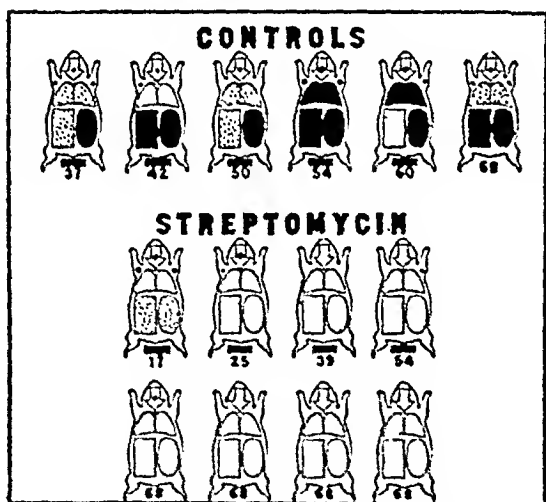
HOMO NO. 4



HOMO NO. 6



HOMO NO. 5



HOMO NO. 7

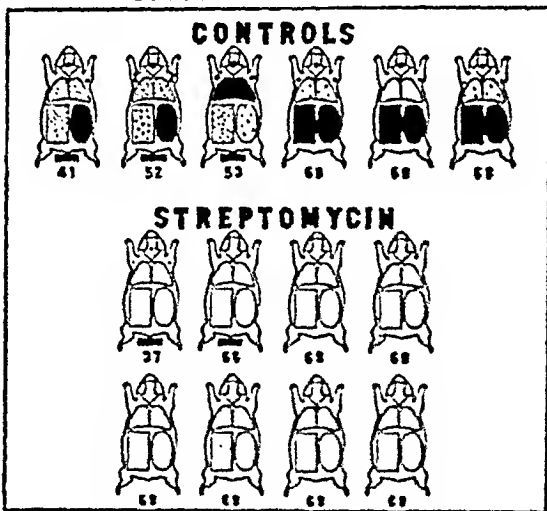


FIG. 3. (Left) Effects of streptomycin therapy in two experiments. The strains of tubercle bacilli were original isolation cultures from patients who had severe, far advanced pulmonary tuberculosis.

FIG. 4. (Right) Effects of streptomycin therapy in two experiments. The inoculum represented original isolation cultures obtained from patients who had severe pulmonary tuberculosis.

lapse of time after infection was sufficient to permit the development in the controls of an impressive amount of disease. In the treated animals the natural progression of the infectious process was markedly interfered with and as a

consequence at necropsy the regressive rather than the progressive phase of the infection was dominant.

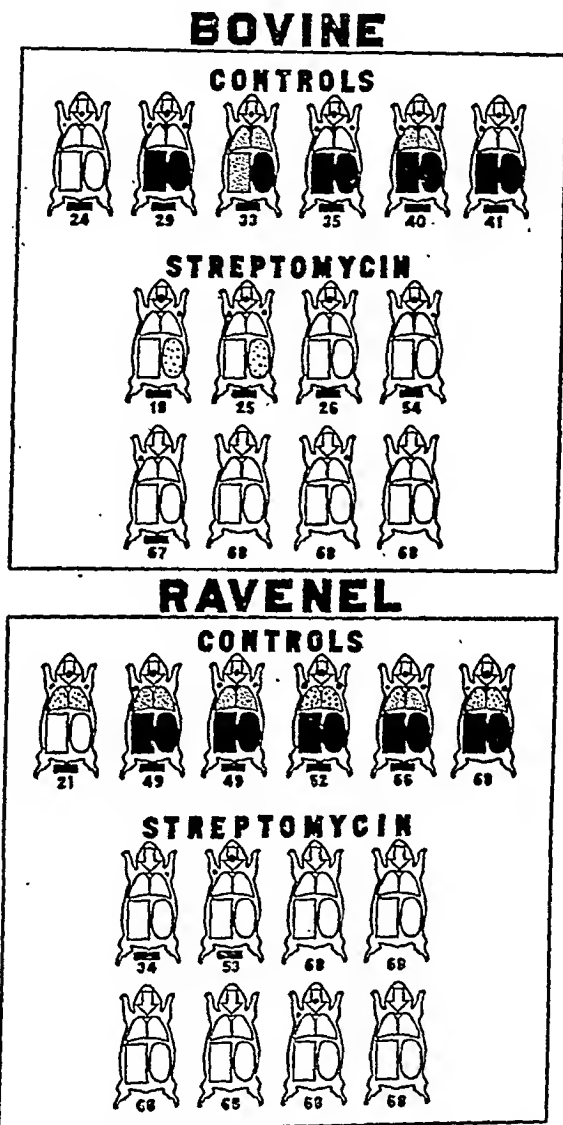


FIG. 5. Results of treating with streptomycin two groups of tuberculous guinea pigs inoculated with tubercle bacilli of the bovine type. Note the severity of the disease in the untreated controls. (Reproduced by permission of J. Roy. Inst. Pub. Health & Hyg.)

Experiments of longer duration would probably have furnished additional information regarding certain important problems related to the effect *in vivo* of streptomycin against the tubercle bacillus. However, evidence obtained after treatment for fifty-four days was sufficiently definitive to indicate that the antagonistic results of streptomycin against the laboratory stock strain

H37Rv could be obtained also against bovine tubercle bacilli and against several previously uncultured strains of tubercle bacilli obtained directly from tuberculous patients. Since the results of therapy against each of the ten strains of tubercle bacilli were comparable, confidence is maintained in the continued use of strain H37Rv as the infective agent in experimental tuberculosis.

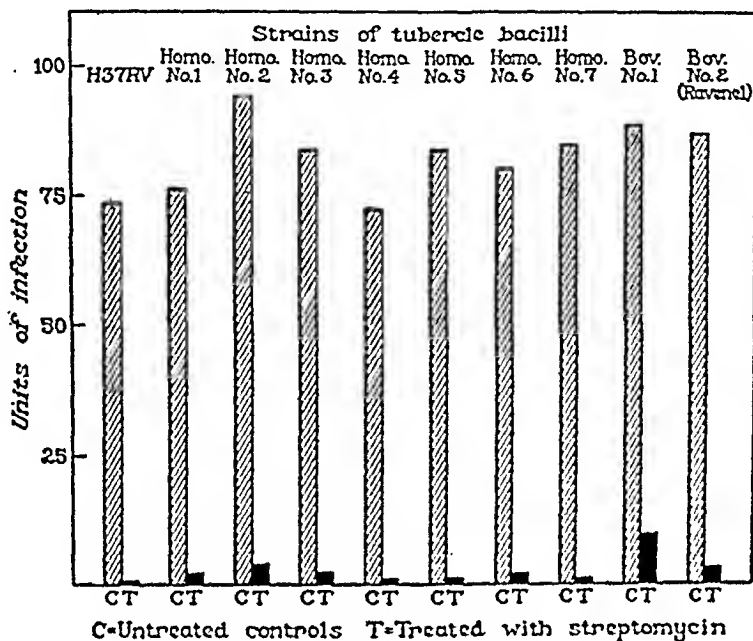


FIG. 6. Summary of relative amounts of tuberculosis, observed microscopically and expressed graphically in units of infection, produced by ten different strains of tubercle bacilli. Each strain was used to inoculate a group of 14 guinea pigs; 8 were treated and 6 were not treated. (Reproduced by permission of J. Roy. Inst. Pub. Health & Hyg.)

SUMMARY AND CONCLUSIONS

To determine the therapeutic antagonism of streptomycin to strains of mammalian tubercle bacilli other than the laboratory stock strain H37Rv, a series of 10 studies was done. Ten groups of 14 guinea pigs each were inoculated, ten different strains of tubercle bacilli being used. These consisted of seven original isolation cultures from 7 patients who had pulmonary tuberculosis, two bovine strains and, for comparison, strain H37Rv. The inoculum for each animal was 0.1 mg. of tubercle bacilli administered subcutaneously. Eight animals in each group were treated. The daily dose of streptomycin per animal was 6 mg. given in four equal doses six hours apart. Medication was started two weeks after inoculation and was continued for fifty-four days.

The results obtained from the 10 studies suggest the following conclusions:

1. The susceptibility *in vivo* of mammalian tubercle bacilli to streptomycin is not strain-specific.

2. Experimental infections produced in guinea pigs by bovine tubercle bacilli are amenable to the antagonistic action of streptomycin.

3. In chemotherapeutic experiments conclusions based on the chemotherapeutic results of infections produced by the laboratory stock strain of tubercle bacilli H37Rv constitute dependable evidence of the degree of antagonism of a given substance for tubercle bacilli of the human type.

SUMARIO Y CONCLUSIONES

La Estreptomicina en la Tuberculosis Experimental

A fin de determinar el antagonismo terapéutico de la estreptomicina a las cepas mamíferas de bacilos tuberculosos distintas de la cepa stock de laboratorio H37Rv, ejecutóse una serie de 10 estudios en que se inocularon 10 grupos de 14 cobayos cada uno, usando 10 cepas distintas de bacilos tuberculosos. Estas comprendían siete cultivos aislados primitivamente de 7 enfermos que tenían tuberculosis pulmonar, dos cepas bovinas, y para comparación, la cepa H37Rv. El inóculo para cada animal consistió en 0.1 mgm. de bacilos tuberculosos administrados subcutáneamente. Se trató a ocho animales de cada grupo, siendo la dosis diaria de estreptomicina por animal 6 mgm. administrados en cuatro dosis iguales a plazos de seis horas. La medicación fué iniciada dos semanas después de la inoculación y continuada durante cincuenta y cuatro días.

Los resultados derivados de los 10 estudios sugieren las siguientes conclusiones:

1. La susceptibilidad *in vivo* de los bacilos tuberculosos de mamífero a la estreptomicina no es específica para cepas.

2. Las infecciones experimentales producidas en los cobayos por bacilos tuberculosos bovinos ceden a la acción antagonica de la estreptomicina.

3. En los experimentos quimioterapéuticos las conclusiones basadas en los resultados terapéuticos alcanzados en las infecciones producidas por la cepa stock H37Rv del bacilo tuberculoso constituyen prueba fidedigna de la intensidad del antagonismo de una sustancia dada hacia los bacilos tuberculosos de tipo humano.

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FREQUENCY OF ADMINISTRATION OF STREPTOMYCIN*

Its Influence on Results of Treatment of Tuberculosis in Guinea Pigs

WILLIAM H. FELDMAN,¹ H. CORWIN HINSHAW² AND A. G. KARLSON¹

The relatively rapid excretion from the body of known antibiotic substances has made it appear desirable to administer drugs such as penicillin and streptomycin at frequent intervals to insure the maintenance of the concentrations in the blood usually considered adequate for therapeutic effects. The presumed necessity for frequent administration of the drugs mentioned entails considerable effort and complicates what is otherwise a simple therapeutic procedure.

Attempts have been made to meet this problem by reducing the rapidity of absorption from the tissues by incorporating antibiotics in various menstrua. In the case of penicillin this has been a fairly satisfactory solution. With streptomycin the quantity of drug required for each daily dose (1 to 3 g. per day for human beings) has constituted an added complicating factor in clinical practice. Special menstrua have been proposed for streptomycin with preliminary results that seem promising (1).

In our previous studies in which streptomycin was administered to tuberculous guinea pigs the drug was injected subcutaneously every six hours (2). This interval between doses was selected more or less arbitrarily despite the fact that streptomycin could not be detected in the blood after more than three or four hours. It seemed important, therefore, to determine whether or not satisfactory therapeutic results might be obtained when the drug was administered at even longer intervals. With this objective the following study was made. Brief reference to this study was made in another publication (3).

METHOD

Sixty-four adult guinea pigs were each inoculated subcutaneously with 0.1 mg. of tubercle bacilli, human strain H37Rv. Twenty-three days later 10 of the animals (group 1) were killed for necropsy to determine the extent of the tuberculous infection. Also on the twenty-third day after inoculation, treatment of four groups (groups 3 to 6) of the infected animals with streptomycin was begun. Each group consisted of 10 animals. The 14 remaining infected guinea pigs served as untreated controls (group 2).

The total dose of streptomycin for the animals that survived until treatment was stopped in the four groups was the same; however, the frequency of administration differed. In group 3 each animal received daily 8 mg. of streptomycin in one dose. In group 4 each animal received daily 8 mg. of streptomycin in two equal doses at twelve-hour intervals. The animals in group 5 received daily 8 mg. of streptomycin in four equal doses at six-hour intervals. In group 6 the animals were treated alternate weeks; each animal received a daily dose of 16 mg. of streptomycin in four equal doses at six-hour intervals.

Treatment was terminated eighty-three days after the animals were inoculated with tubercle bacilli. The duration of treatment was sixty days.

* Streptomycin utilized in this study was supplied through the courtesy of Dr. D. F. Robertson, Merck and Company, Rahway, New Jersey.

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The presence or absence of tuberculosis in the organs of predilection was recorded at the time of necropsy. In addition, the tissues of all of the animals were subsequently examined microscopically and the numerical index of infection for each determined (table 1). This method of recording the extent and the morphological character of experimental tuberculous infections has been described previously (4).

TABLE 1

Results of microscopic determination of relative degree of tuberculosis expressed numerically

GROUP	INTERVALS OF TREATMENT	ANIMALS*	SPLEEN (MAX.: 35)	LUNG (MAX.: 30)	LIVER (MAX.: 25)	SITE OF INOCULATION (MAX.: 10)	AVERAGE INDEX OF INFECTION (MAX.: 100)
1	Not treated	10 ¹	21.5	11.0	17.0	10.0	59.5
2	Not treated	14 ²	32.6	20.7	22.0	10.0	85.3
3	Once daily	9 ³	0.4	2.5	0.6	1.5	5.0
4	Twice daily	9 ⁴	0.6	1.4	0.11	0.12	3.2
5	Four times daily	8 ⁵	1.3	1.5	1.1	0.37	4.2
6	Once daily, alternate weeks	6 ⁶	2.1	0.66	0	3.3	6.0

* In the treated groups only animals are included that received treatment for at least three weeks.

¹ Killed on the twenty-third day following infection.

² Seven died before the eighty-third day following infection; survivors killed on the eighty-third day.

³ All but 2 animals died before the eighty-third day following infection.

⁴ Same as group 3.

⁵ All but one animal died before the eighty-third day following infection.

⁶ All but 4 animals died before the eighty-third day following infection.

RESULTS

Controls: (Group 1) The 10 guinea pigs in group 1 were killed for necropsy on the twenty-third day after being inoculated with tubercle bacilli. Evidence that the infection had disseminated widely from the site of inoculation was found in all. In all instances severe tuberculous involvement of the spleen was observed. In a few of the animals evidence of the disease was apparent grossly in the liver and lungs (figure 1a). Microscopically the spleen, liver and lungs of all the guinea pigs in this group were tuberculous. The average numerical index of infection for the 10 animals in this group, based on a theoretical maximal index of infection of 100, was 59.5 (table 1).

It is a reasonable presumption that the amount of tuberculosis observed in these 10 guinea pigs represented a fair indication of the virulence of the inoculum and the extent to which the disease had developed in a period of approximately three weeks. The evidence obtained—both grossly and microscopically—suggested that the animals in the groups that were treated were affected with widely disseminated, progressive, destructive tuberculosis before treatment was begun. Thus, conditions existing in the animals that were treated were formidable and not likely reversible without the aid of a potent remedial factor.

(Group 2) In group 2, all 14 animals received no treatment and those that were alive on the eighty-third day were killed. At necropsy the expected results of infection of guinea pigs with virulent tubercle bacilli were obtained (figure 1*b*). Of the 14 animals, 7 died, presumably as a result of the tuberculous infection, before the eighty-third day. Grossly, 6 of these had severe tuberculosis of the liver, spleen and lungs. On gross examination the liver and spleen of the seventh animal appeared to be tuberculous, but in the lungs the disease was detectable only microscopically. Of the 7 animals in group 2 that were killed on the eighty-third day, a similar degree of tuberculosis was noted grossly in 5,^f while

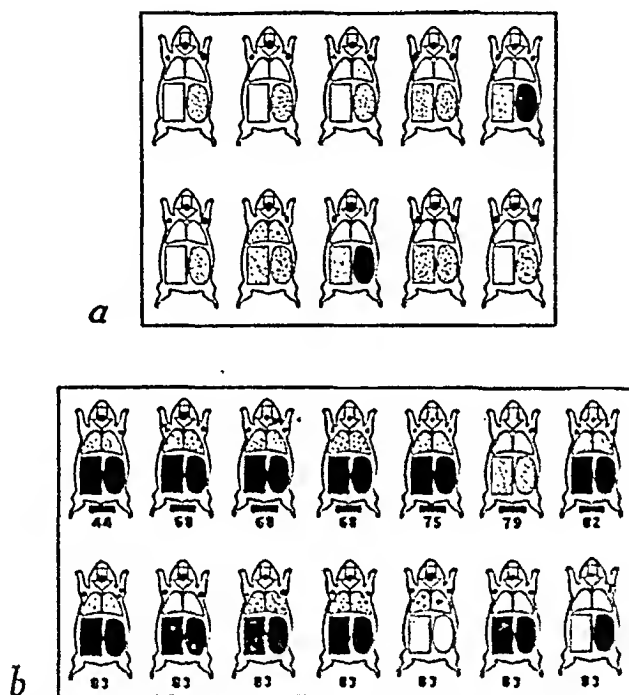


FIG. 1. The amount of tuberculosis, recorded schematically, observed grossly; (a) group 1, pretreatment controls; (b) group 2, post-treatment controls. The small numbers below each animal indicate the number of days after inoculation that death occurred. (Reproduced by permission of J. Roy. Inst. Pub. Health & Hyg., London.)

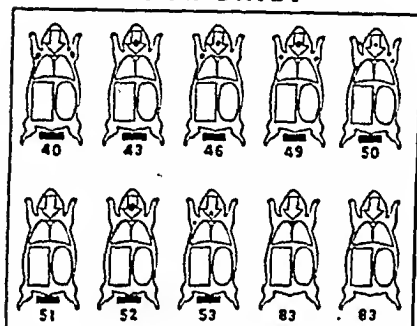
on gross examination of the remaining 2 animals the disease appeared to be limited to the spleen in one and the lungs in the other. The amount and character of tuberculosis in group 2 were determined microscopically. The average index of infection expressed numerically was determined to be 85.3 (table 1). This figure is indicative of a rather severe wide-spread infection.

Comment: The gross and microscopic findings in groups 1 and 2 constitute impressive evidence that, after inoculation of the animals with this large dose of virulent tubercle bacilli, a well-advanced progressive disease had become established when treatment of groups 3, 4, 5 and 6 was begun. Furthermore, the evidence indicates adequately that a nonreversible infection with lethal potentialities developed in animals that were inoculated but not treated.

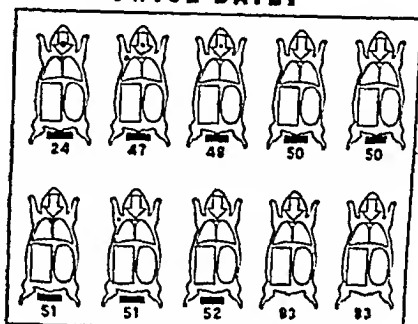
Treated animals: (Group 3, treated once daily) In interpretation of the results of treatment only animals that received streptomycin for three or more weeks were considered. In group 3, none of the animals had gross signs of tuberculosis in the liver and spleen or lungs at necropsy. In some, evidence of residual disease was observed at the site of inoculation in the subcutaneous tissue over the sternum (figure 2). Microscopically the average index of infection for the 9 animals that received treatment for three weeks or longer, was recorded as 5.

TREATED AFTER 23 DAYS

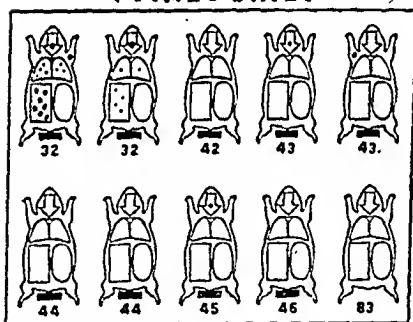
ONCE DAILY



TWICE DAILY



4 TIMES DAILY



ALTERNATE WEEKS

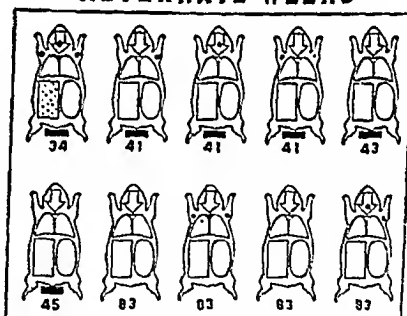


FIG. 2. The amount of tuberculosis, recorded schematically, noted at the time of necropsy in the respective groups of treated animals. The small numbers below each animal indicate the number of days after inoculation that death occurred. (Reproduced by permission of J. Roy. Inst. Pub. Health & Hyg., London.)

This was in marked contrast to the average index of infection for the group of untreated controls which was 85.3 (table 1).

Although tubercle bacilli were isolated on culture from the spleens of 7 of the 9 treated animals, in 2 instances the results of the attempts to culture tubercle bacilli from the spleen were negative. In neither of these 2 animals was tuberculosis found in the liver, spleen or lungs, grossly or microscopically.

(Group 4, treated twice daily) Nine animals in this group received streptomycin for three weeks or longer. On gross examination little evidence of tuberculosis was found at the time of necropsy (figure 2). Microscopically the same condition prevailed, the average index of infection for the group being 3.2

(table 1). Cultures for tubercle bacilli were made from the spleens of 8 of the 9 treated guinea pigs and all were positive for tubercle bacilli. Aside from the fact that fewer animals in group 4 had residual lesions at the site of inoculation than animals in group 3, no significant difference was apparent in the therapeutic results in the two groups.

(Group 5, treated four times daily) In group 5, 8 animals received streptomycin for three weeks or longer. The result of treatment in these 8 animals was quite comparable to the results recorded in group 4. Little evidence of tuberculosis was observed grossly (figure 2) and the average index of infection for the group as determined microscopically was 4.2 (table 1). Cultures of tubercle bacilli were obtained from the spleens of 7 of the animals; in one, splenic culture was negative.

(Group 6, treated alternate weeks) Of the 10 animals in this group living when treatment was started, 4 died before they had been treated for three weeks. Grossly little evidence of tuberculosis was observed in the 6 animals that were treated for three weeks or longer (figure 2). Microscopically, evidence of active tuberculosis of minimal extent was found in the spleen of one animal. In 2 other animals small inactive lesions were found in the spleen of one animal and in the lung of the other. The average index of infection for this group was recorded as 6. Tubercle bacilli were obtained in cultures of material from the spleen of 5 of the 6 animals that were treated. In one animal splenic cultures remained negative.

MORTALITY

Compared with previous experiences with chemotherapy in tuberculous guinea pigs, the mortality of the animals that received treatment was rather unusual. Thirty-one (77.5 per cent) of the treated animals died during the study. Eight of the animals died before they had been treated for a minimum of three weeks. Twenty-three animals that received treatment for three weeks or longer died before treatment was terminated sixty days after it was begun. Only 9 of the treated guinea pigs survived. These were killed at the end of the study. The average survival time of the animals in group 2 that died was sixty-nine days. This figure is in marked contrast to the average survival time of forty-four days for the treated animals that died before treatment was stopped.

At necropsy evidence of massive hemorrhage in the abdominal cavity was found, without exception, in the animals of groups 3, 4, 5 and 6 that died. Investigation of the cause of the hemorrhage revealed that a similar state could be produced readily if guinea pigs were restrained improperly at the time of injection. When this fact was recognized and the animals receiving treatment were handled accordingly, no further deaths occurred.

Results indicate that death of a large percentage of the animals that were treated did not preclude the accomplishment of a rather satisfactory therapeutic effect during the relatively short period of treatment. Of much importance in this respect was the rather formidable amount of disease presumably present in the treated animals when treatment was started. Examination of the 10 animals

killed before the beginning of treatment without exception showed that the infection had become well established in the liver, spleen and lungs (figure 1). It appears likely that the disease was present in a comparable degree in the 40 treated animals when treatment was started.

COMMENT

The results of these observations provide reason for further investigation of the frequency of medication in chemotherapy of tuberculosis. The results of the administration of promin intermittently to tuberculous guinea pigs have been published previously (5). In the case of streptomycin the necessity of the maintenance of appreciable concentration in the blood in order to insure therapeutic effectiveness may well be questioned.

The explanation for the therapeutic effectiveness of a single dose of streptomycin given at twenty-four-hour intervals or at six-hour intervals every other week is not apparent. Certainly the results were unexpected. A possible explanation follows. A few hours after administration of streptomycin a high percentage (75 to 80 per cent) of the drug is excreted by the kidneys. In tuberculosis perhaps a sufficient amount of the drug adheres to the surface of the bacterial cells or remains in immediate contact with the bacteria and adjacent tissues to exert a more or less constant repressive influence for a considerable time after all detectable amounts of the drug have disappeared from the blood. Perhaps the concentration of streptomycin in the tissues is as important in a slowly progressive infection like tuberculosis as is the concentration in the blood. It is possible that a single daily and rather brief exposure of the bacterial cell to streptomycin may be sufficient to so disturb the reproductive mechanism of the tubercle bacillus as to require several hours to several days for the bacillus to recover its reproductive equilibrium.

It may be presumed that during this period of antagonistic activity progression of the morbid reaction is either diminished or stopped. If the antagonistic action is repeated frequently enough, it is logical to believe that eventually the reparative factors of the involved tissues are able to attain ascendancy over the pathogenic factors. When this occurs, the infection is arrested and the subsequent course of the disease will depend largely on the intrinsic susceptibility or resistance of the host.

The significance of these observations is of considerable importance. Since the results of this study failed to indicate the necessity of administering streptomycin at six-hour intervals, we have, in subsequent work, routinely administered the drug to tuberculous guinea pigs in two doses daily twelve hours apart. We use a total daily dose of 6 mg. per animal. The results of treatment of tuberculous guinea pigs on this schedule have been entirely consistent with those recorded in this report. The therapeutic effects have been in no way inferior to those obtained in earlier work in which the drug was given four times daily.

These findings should be of interest to the clinician. Possibly for certain types of clinical tuberculosis the schedule of administration of streptomycin could be

revised without adversely influencing the therapeutic results. This possibility is being investigated.

PRELIMINARY CLINICAL OBSERVATIONS

Efforts to extend these observations to clinical practice are now under way on a limited scale. Five patients who have tuberculosis have received 1.0 g. of streptomycin intramuscularly twice a day for from one to four months. No unfavorable reactions followed such injections and the usual delayed toxic effects which have been observed (6) have not varied significantly from those encountered in cases in which patients received the same daily dose in several injections. Two of these 5 patients have been treated for a sufficient period to allow observation of the therapeutic effects which were attributed to streptomycin.

It should be emphasized that clinical observations are not yet sufficiently complete to warrant alteration of the usual schedule of administration. Until they are complete we continue to recommend injections every three to six hours in treatment of clinical tuberculosis.

Due consideration should be given to the possibility that infrequent administration of streptomycin might facilitate the appearance of drug resistant strains of tubercle bacilli. No observations have been made which would support this suggestion. On the contrary, it has been observed that frequent administration of large doses of streptomycin does not prevent the appearance of drug resistant strains of tubercle bacilli in certain cases.

SUMMARY

Observations of the influence of different schedules of administration of streptomycin on treatment of tuberculosis in 64 guinea pigs are recorded. All of the animals were inoculated subcutaneously with 0.1 mg. of tubercle bacilli, human type (H37Rv). Extensive tuberculosis developed in 10 animals that were killed on the twenty-third day after inoculation. Four groups of 10 animals each were used to determine the effect of different schedules of administration on treatment. The total amount of streptomycin administered was the same for each animal that lived till the eighty-third day. Treatment was started on the twenty-third day after inoculation. In groups 3, 4 and 5, the daily dose was 8 mg. The schedule of administration of streptomycin varied. In group 3 the animals received the drug in one dose given daily; in group 4 two doses were given daily; in group 5 the drug was given four times daily at six-hour intervals. In group 6 the daily dose of streptomycin was doubled and administered every six hours. However, the animals in group 6 were treated only alternate weeks. A group of 14 infected guinea pigs (group 2) served as untreated controls. The duration was eighty-three days. In addition, a few observations on administration of streptomycin twice daily to patients with clinical tuberculosis are mentioned.

The data concerning the marked efficiency of streptomycin in combating previously established tuberculosis in guinea pigs were consistent with data reported previously.

In our study of tuberculous guinea pigs administration of streptomycin at frequent intervals during each twenty-four hours was not essential to successful therapeutic results. In tuberculous guinea pigs administration of streptomycin twice daily at twelve-hour intervals seemed adequate. The eventual suppression of the disease was striking and consistent.

When guinea pigs were inoculated with tubercle bacilli three weeks before treatment was started, the condition which developed was markedly improved within a relatively short time (three to four weeks) by administration of streptomycin.

The results suggest the importance of a critical examination of the present schedule of streptomycin therapy in clinical tuberculosis. In the absence of adequate data it would appear advisable at present to continue to administer streptomycin at frequent intervals in cases of tuberculosis. However, large doses given infrequently are well tolerated by human beings.

SUMARIO

La Frecuencia de la Administración de la Estreptomicina. Su Influjo sobre el Resultado del Tratamiento de la Tuberculosis en el Cobayo

Preséntanse observaciones acerca del influjo de distintos horarios de administración de la estreptomicina en el tratamiento de la tuberculosis en 64 cobayos. A todos los animales se les inoculó subcutáneamente 0.1 mgm. de bacilos tuberculosos de tipo humano (H37Rv). En 10 animales matados al 23° día de la inoculación se observó tuberculosis extensa. Usáronse cuatro grupos de 10 animales cada uno para determinar el efecto de diversos horarios de administración sobre el resultado del tratamiento. La dosis total de estreptomicina administrada fué idéntica para cada animal que sobrevivió hasta el 83° día. El tratamiento se inició el 23° día consecutivo a la inoculación. En los grupos 3, 4 y 5 la dosis diaria fué de 8 mgm., variando el horario de administración de la estreptomicina. En el grupo 3 los animales recibieron la droga en una dosis diaria, en el grupo 4 en dos dosis diarias, y en el grupo 5 en cuatro dosis diarias a plazos de seis horas. En el grupo 6 se dobló la dosis diaria, administrándose cada seis horas, pero sólo se trató a los animales en semanas alternadas. Un grupo (el 2) de 14 cobayos infectados constituyó los testigos no tratados. El experimento duró 83 días. Menciónanse, además, algunas observaciones relativas a la administración de la estreptomicina dos veces diarias a enfermos con tuberculosis clínica.

Los datos referentes a la pronunciada eficacia de la estreptomicina para combatir una tuberculosis previamente establecida en los cobayos armonizan con los presentados anteriormente.

En este estudio de cobayos tuberculosos la administración de estreptomicina a plazos frecuentes cada 24 horas no resultó indispensable para el éxito terapéutico, pareciendo adecuada la administración dos veces diarias a plazos de 12 horas. La supresión eventual de la enfermedad fué notable y constante.

Cuando se inoculó a los cobayos con bacilos tuberculosos tres semanas antes de iniciar el tratamiento, el estado evocado mejoró decididamente en un plazo

relativamente breve (tres a cuatro semanas) con la administración de estreptomina.

El resultado indica la importancia de realizar un estudio analítico de los horarios actuales de la estreptomycinoterapia en la tuberculosis clínica. A falta de datos adecuados parece conveniente continuar por ahora administrando la estreptomina a plazos frecuentes en casos de tuberculosis. Sin embargo, las dosis masivas administradas de tarde en tarde son bien toleradas por los seres humanos.

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SIMULTANEOUS SAMPLES OF ALVEOLAR AIR FROM EACH LUNG AND PARTS THEREOF^{1,2}

A Preliminary Report of a Method Using Bronchial Catheterization

GÖSTA BIRATH

In experiments on animals, catheterization of the trachea has long been used to obtain alveolar air. The last portion of the expiratory air has then been collected and the samples pooled in order to have an amount sufficient for analysis. In this way it has been possible to obtain reliable values. Samples of alveolar air have also been taken from the bronchi of animals (Kramer and Sarre, 1936).

Loewy and Schrötter (1905) carried out catheterization of human bronchi with silver tubes *via* bronchoscope. By means of a rubber cuff that could be inflated around the distal end of the catheter the bronchus was entirely cut off from communication with the outside air. The samples of air that were obtained from the part of the lung cut off from the outside air were in a state of tension equilibrium with the blood gases in the venous system. Such samples had no connection—as is otherwise the case with samples of alveolar air—with the free gas exchange in the lungs. The authors found it worthy of note *wie tolerant sich die Schleimhaut der Bronchien gegenüber eingeführten Instrumenten erwies*.

Bezançon, Braun, Soulas, Guillaumin and Cachin (1936) made use of a similar arrangement involving the cutting off of one of the main bronchi, but allowing free respiration through the catheter, and collected expiratory air for examination. In this way they determined ventilation, carbon dioxide excretion and oxygen consumption from each lung separately; but this method is inferior to the bronchspirometry worked out by Björkman (1934), in which the same values were registered spirometrically. The examination of alveolar air from each lung separately has not, as far as I have been able to find, been carried out on man before.

The principle of the method here described is that, through a fine catheter passed down into the bronchial tree, a small part of the last expiratory air is removed by careful suction from a receptacle filled with mercury under ordinary respiration. The small amount of air that is obtained in this way on every respiration is repeatedly collected in the receptacle until the amount suffices for analysis.

The essential conditions that must be fulfilled if representative alveolar air samples are to be obtained are in the main as follows:

(1) The catheter introduced must not block the bronchial lumen and it must narrow its lumen as little as possible. With marked narrowing, ventilation in the part of the lung concerned will be impaired as it is in bronchostenosis, and the values of the gaseous composition of the alveolar air will be altered.

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² This study was made under a grant from the Swedish National Union against Tuberculosis.

(2) The amount of air that is removed at the end of each expiration must not be too great and it must not be aspirated too rapidly. Otherwise, one risks aspirating respiratory air from other bronchi.

(3) The respiration throughout the examination should not be so affected that the alveolar air is changed in composition (for example by hyperventilation).

(4) The ventilation in the lung examined must not be reduced beyond the point at which alveolar air, during the last part of the expiration, streams through the bronchus in which the catheter is placed.

The catheters used have been the ordinary contrast-bearing ureteral catheters, numbers 5 to 7, which are suitable both in length and diameter. The narrowest, number 5, have been provided with an extra perforation for aspirating the sample, but, nevertheless, they easily stick by suction to the bronchial wall. One advantage of these catheters is that they are graduated, so that one always knows how far they have been introduced. After each examination the catheters were sterilized—after mechanical cleaning—by immersing them for thirty minutes in a 5 per cent chloramine solution.

PROCEDURE

The mucous membranes of the nose and pharynx are anesthetized and a few drops of the anesthetic (2 per cent decicain) are injected into the bronchi. The catheters are then introduced through the nostrils. They are held in the pharynx and led into the larynx. In general, the catheter introduced through the right nasal passage runs into the left main bronchus and *vice versa*. When the catheter is introduced about 25 cm., it is at the carina, and it is only after this that one can count on its having entered one of the main bronchi. By fluoroscopy or eventually X-ray photography, one must ascertain the exact position of the catheters. If irritation provokes cough, a further small amount of the anesthetic may be injected through the catheter. When the catheters are in the desired position they are fixed with adhesive plaster to the nostrils.

One begins to take samples after the patient has been allowed to rest for five to ten minutes, or possibly longer, following the roentgen examination. At first, a small amount of air is aspirated in order to rinse the "dead space" of the apparatus (chiefly the catheter). This amount of air, like the definitive sample, is obtained by means of quick turns of the tap of the receptacle, so that only a small part of the last portion of the expiratory air is aspirated. With this procedure it is possible, without difficulty, during quiet respiration, to obtain the sample from the last third or fourth part of the expiratory air.

DISCUSSION

Under normal conditions one may expect that the air remaining in the bronchi at the end of inspiration is completely washed out during the last third of expiration. One may thus rely upon the sample's consisting of pure alveolar air; but it is not equally certain that this will be the case under pathological conditions, for if the tidal air is considerably decreased, the respiratory "dead space" will be

relatively larger as compared to the tidal air. It will, then, be no longer possible to assume that the last part of the expiratory air, even in the bronchi, will consist of pure alveolar air. This is so in spite of the fact that the size of the "dead space" is normally very small in relation to the expired alveolar air, when the sample is taken in the bronchi. Under certain conditions the respiratory excursions on one side may conceivably (for example owing to marked pleural retraction, with or without pneumothorax) be so small that the stream of air in the bronchi will consist mainly of the air of the "dead space." Markedly reduced ventilation is an obstacle to the obtaining of alveolar air with the method described here.

Another possible source of error is that the examination in itself might possibly cause hyperventilation; but, as is seen from the low respiratory quotients of the examples given below, this danger seems to be relatively slight.

By placing the catheters in different positions it should be possible to draw comparisons between the two lungs and between a lower lobe and the lung as a whole. It should be possible to ascertain interesting facts concerning the physiology of respiration under pathological conditions. It also ought to be possible to use the method when, for some reason, the taking of samples of alveolar air according to the Haldane-Priestley method is not feasible.

EXAMPLES

Case R. K. had extensive tuberculous parenchymal lesions throughout the right lung as well as small cavities. There were lesions of moderate extent in the left apex. Pneumothorax treatment was started on the right side about six weeks before bronchial catheterization. The lung was then adherent at the apex but selectively collapsed in the upper part of the lower lobe, otherwise there was moderate collapse. Catheters were introduced, one into the right main bronchus and one into the trachea just above the carina. In table 1 are shown the results that were obtained on double determinations (table 1, I and II).

It is rather uncertain whether the air obtained in this case is pure alveolar air. The surprising finding of lower oxygen values and higher carbon dioxide values in the trachea than in the right main bronchus is evidently due to admixture of alveolar air from the left lung to the sample taken in the trachea. It is possible that in the right pneumothorax lung, owing to reduced respiratory excursions, the "dead space" may be larger, which might explain the difference. Another, more probable, explanation is that the exchange of gases takes place to a lesser extent, with a poorer utilization of the oxygen and reduced carbon dioxide excretion in the pneumothorax lung (cf. Leiner, 1944). A more detailed discussion of such a case will not be possible until more cases have been studied.

Case N. A. had scattered, fresh tuberculous parenchymal lesions and cavities in both lungs. Pneumothorax was induced on both sides one and two months before bronchial catheterization. The lungs were free of adhesions, with the possible exception of the right side, where pneumothorax had first been induced. In the right pleural space, a slight exudate had formed, which may have caused basal adhesions. With one catheter samples were taken from the right main bronchus and with the other one from the left lower lobe.

The samples taken from the left lower lobe showed the lowest oxygen content and the highest carbon dioxide amount (table 2). This may indicate either that the samples obtained from the right main bronchus were not really alveolar air or that the alveolar air has a different composition in different parts of the lungs.

The carbon dioxide content of the alveolar air in the left lower lobe favors the assumption of an increased sensibility of the respiratory centre to the carbon dioxide tension in the blood in cases with bilateral pneumothorax, for the carbon dioxide tension is in this case only 33 mm., that is, lower than the normal value of about 40 mm. There is reason to believe that such an increased sensibility actually exists, though further investigations into the matter are of course necessary, especially since, due to the low respiratory quotient in this case, it is possible that the carbon dioxide tension was reduced after hyperventilation during the introduction of the catheters.

TABLE 1

Bronchial catheterization of a case with right-sided induced pneumothorax

SAMPLE TAKEN FROM	EXPERIMENT	CARBON DIOXIDE	OXYGEN	RESPIRATORY QUOTIENT
		<i>per cent</i>	<i>per cent</i>	
Right main bronchus	I	4.14	15.55	0.77
	II	4.50	15.00	0.76
Trachea	I	4.91	14.33	0.75
	II	5.01	14.61	0.82

TABLE 2

Bronchial catheterization of a case with bilateral pneumothorax

SAMPLE TAKEN FROM	CARBON DIOXIDE	OXYGEN	RESPIRATORY QUOTIENT
	<i>per cent</i>	<i>per cent</i>	
Right main bronchus	4.42	14.79	0.72
Left lower lobe	4.80	14.00	0.71

SUMMARY

In order to obtain alveolar air from each lung, bronchial catheterization has been carried out with contrast-bearing ureteral catheters and under roentgenological control to insure correct placing. Alveolar air has been obtained in this way also only from the lower lobe. An account is given of 2 patients with pulmonary tuberculosis treated with pneumothorax.

SUMARIO

A fin de obtener aire alveolar de cada pulmón se llevó a cabo un cateterismo bronquial con sondas ureterales que contenían sustancias opacas, bajo fiscalización roentgenológica a fin de garantizar la colocación adecuada. También se obtuvo en la misma forma aire alveolar exclusivamente del lóbulo inferior. Preséntase una reseña de dos tuberculosos pulmonares tratados con el neumotórax.

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PULMONARY TUBERCULOSIS SIMULATING BRONCHOGENIC CARCINOMA¹

A Report of Four Cases

ANIBAL ROBERTO VALLE AND M. LAWRENCE WHITE, Jr.

Not always can an exact preoperative diagnosis of bronchogenic carcinoma be established. Differential diagnosis cannot be made on the basis of the clinical picture alone, as the symptoms and signs are common to chronic inflammation, tuberculosis and lung abscess as well as bronchogenic carcinoma. Positive diagnosis can be established by bronchoscopic biopsy in approximately 70 per cent of the cases (6, 7, 9). In most of the remaining 30 per cent a definite diagnosis can be made only after exploratory thoracotomy.

Much has been written about bronchogenic carcinoma simulating other chest diseases, but few authors have reported cases in which other chest lesions simulate bronchogenic carcinoma.

Graham and Singer (4) report 3 cases of calcified pulmonary tuberculosis; Haight and Farris (5), a case of tuberculoma; Bradshaw and Chodoff (1), a case of anthracosilicosis; Rendich and Camiel (8), 2 cases of silicosis; Freedlander and Wolpaw (3), 4 cases of chronic inflammatory disease; Brown and Biskind (2), and Singer and Tragerman (10), one case each of lipoid pneumonia, all simulating bronchogenic carcinoma. We present 4 recent cases in which the clinical diagnosis was bronchogenic carcinoma in spite of negative bronchoscopic examinations. At exploratory thoracotomy tissue for examination was removed and a diagnosis of tuberculosis returned in 3 cases, and chronic inflammation with probable healed tuberculosis in the other. These are the only 4 cases we have explored suspecting a bronchogenic carcinoma in which the suspicion was not corroborated by operative findings.

CASE REPORTS

Case 1: W. H., a 56-year-old colored male, was admitted to the University of Virginia Hospital on August 27, 1945 with a history of productive cough of several weeks' duration. The sputum was mucoid and moderate in quantity. He had had several small hemoptyses and one pulmonary hemorrhage of about 200 cc. within the two weeks prior to admission. There had been no significant weight loss.

Physical examination was essentially negative except for a few rales over the right upper and middle lobes anteriorly. No lymph nodes were palpable. Roentgen studies of the chest showed an area of pneumonitis and apparent atelectasis of the lower part of the right upper lobe and the middle lobe (figure 1). Bronchograms showed a block of the right middle lobe bronchus about 2 cm. from the main bronchus. Fluoroscopic examination revealed normal diaphragmatic function. Six sputum concentrates were negative for tubercle bacilli. Because he had worked in a granary, the sputum was examined for fungi, also with negative findings. The blood count showed 13.6 million red cells and 6,600 white cells. Urinalysis revealed 6 to 10 pus cells and occasional red blood cells per high

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FIG. 1. (Upper left.) Case 1. A dense mass is seen extending from the hilum to the periphery of the right lung.

FIG. 2. (Upper right.) Case 2. A homogeneous area of increased density is seen in the left apex. On earlier films taken before admission this mass was seen to become progressively larger.

FIG. 3. (Lower left.) Case 3. A dense hilar mass is seen on the right with a light infiltration in the midlung zone.

FIG. 4. (Lower right.) Case 4. An area of density with central cavitation is seen in the midlung zone of the right lung.

power field. Bronchoscopic examination was negative except for the presence of blood arising both from the right upper and right middle lobe bronchi.

Operation: On September 17, 1945, through a posterolateral approach, a right exploratory thoracotomy was carried out under intratracheal nitrous oxide-ether anesthesia. The pleural cavity was entered through the periosteal bed of the resected sixth rib. No fluid was present. The upper and middle lobes were found adherent to the chest wall and were freed by blunt dissection. A hard mass, the size of an orange, involving the lower portion of the upper lobe and upper portion of the middle lobe was found. Several hard enlarged lymph nodes were found anterior and posterior to the hilum. One of these was about the size of a walnut. The hilar vessels were inaccessible and the case was considered a technically inoperable carcinoma. Several biopsies were taken, both from the mass in the lung and from the lymph nodes, and the chest was closed without drainage after 50,000 units of penicillin had been instilled in the pleural space.

Pathological report: "There are sections of three nodules. Two of these consist of well encapsulated dense hyalinized and pigmented connective tissue. The other nodule is made of dense but cellular connective tissue, in which there are ovoid-shaped zones of necrosis which are surrounded by a layer of epithelioid cells and lymphocytes. The lung sections show a slightly thickened pleura which is infiltrated with lymphocytes. The pulmonary alveoli over large areas are replaced by connective tissue, and others are filled with vacuolated monocytes. Throughout there are small tubercles, some caseous and others consisting of epithelioid cells and giant cells. These tuberculous lesions are active and appear fairly young. Although they are located in areas of old organized pneumonia, the two processes appear to be unrelated. The areas of organized pneumonia show no destruction of alveolar walls, but are organizations of intra-alveolar exudate and do not appear to be of tuberculous origin. Diagnosis: Lung showing small scattered areas of tuberculosis of miliary size, organizing nontuberculous pneumonia, caseous and calcifying tuberculous lymphadenitis." The tissue was not stained for acid-fast organisms.

The postoperative course was uneventful. The patient was transferred to a sanatorium and, at last report in November, 1945, he was doing well clinically and his roentgenograms showed improvement.

Comment: The age of the patient, his productive cough, hemoptyses and roentgenographic studies including bronchograms were indicative of bronchogenic carcinoma. The negative bronchoscopy was thought due to the fact that the lesion was beyond the range of the bronchoscope. That the vocal cords moved normally, that the diaphragm was not paralyzed and that there was no pleural fluid and no palpable peripheral lymph nodes were taken as evidence of an operable lesion. It is striking that, in spite of the repeatedly negative sputum examinations in the presence of a productive cough, the lesion was tuberculous.

Case 2: L. B., a 58-year-old white woman, was admitted to the University of Virginia Hospital on April 30, 1945. She had been well until October of 1944 when she developed a respiratory infection, characterized by a dry cough, fever and weakness. In November her cough became productive of mucopurulent sputum and small hemoptyses occurred sporadically. Wheezing was fairly constant. She had sustained a weight loss of about 40 pounds.

Physical examination revealed a decrease in breath sounds and fine moist and distant rales, both anteriorly and posteriorly over the left upper chest. No palpable lymph nodes were present. Laboratory data were essentially negative except for a slight anemia.

Two sputum examinations by direct smear were negative for tubercle bacilli. More examinations were not deemed necessary because of the appearance of the roentgenograms mentioned below. Three serial roentgenograms of the chest taken before admission revealed a gradually enlarging mass in the left upper lobe. The films after admission (figure 2) showed still further concentric enlargement of the density, characteristic of neoplastic growth. Fluoroscopic examination revealed normal diaphragmatic motion. Bronchoscopic examination revealed a marked displacement of the left bronchial tree toward the left; so much so, that the left upper lobe bronchus could not be well visualized. The mucosa of the left main stem bronchus was somewhat thickened and a biopsy was taken. This was negative for carcinoma and tuberculosis.

Operation: On May 4, 1945, the left chest was explored through a posterolateral approach, resecting the fifth rib. No fluid was found in the pleural space. A hard mass occupied most of the left upper lobe except for the lingula. The mass was typical of malignancy in its firmness and its apparent invasive nature. Numerous dense adhesions attached the mass to the thoracic dome. Several hard lymph nodes were palpated adjacent to the arch of the aorta and in the pulmonary ligament. After dividing the apical adhesions and mobilizing the upper lobe, the pulmonary artery was found to be surrounded by friable tissue, apparently neoplastic. The lesion was deemed inoperable and biopsies were taken from the pulmonary mass and from the lymph nodes. The chest was closed without drainage after injecting 50,000 units of penicillin into the pleural space.

Pathological report: "Scattered throughout the lung there are small tubercles; some of these are caseous and others consist only of epithelioid cells and giant cells. The pulmonary alveoli in some areas are filled with mononuclear phagocytes; other areas contain fibroblasts and others contain air. Sections from the lymph nodes contain many characteristic tubercles in all stages of development. Acid-fast stains reveal many tubercle bacilli in both the lung and the nodes. Diagnosis: Tuberculosis of lung and lymph nodes."

The patient's postoperative course was uneventful and she was discharged on the thirteenth day following operation. At last report in November, 1945, with only bed-rest as treatment, the patient was asymptomatic, had gained weight, and the roentgenographic shadow had almost disappeared.

Comment: This patient's age, the history of productive cough with small hemoptyses, the weight loss of 40 pounds, wheezing and the X-ray picture, all strongly suggested bronchogenic carcinoma. Tuberculosis was felt to have been excluded by the negative sputum examinations. Although no tumor was demonstrated at bronchoscopy, the distortion of the upper lobe bronchus was suggestive of malignancy. Even after establishing a diagnosis of tuberculosis, there was still doubt as to whether or not there was a coexisting neoplasm until the follow-up films showed almost complete regression of the lesion.

Case 3: W. B., a 29-year-old white male, was admitted to the University of Virginia Hospital on July 30, 1945, with a history of having coughed up small amounts of blood sporadically for six weeks. A mild dry cough had been present for several months and, since the hemoptyses began, he had produced small amounts of purulent sputum with the cough. There had been no weight loss, no chest pain and no wheezing. His local doctor had suspected tuberculosis, but both sputum examinations and the tuberculin test were negative. One week after the onset of the hemoptyses, he was admitted to a tuberculosis sanatorium where repeated examinations of the sputum, even by culture, were negative. These

negative findings prompted his admission to the University Hospital with a diagnosis of a pulmonary malignancy.

Physical examination in the University of Virginia Hospital disclosed a small area of dullness over the right hilar region with diminished breath sounds in this region. Fine moist râles were heard in the right midlung field. Several small, freely movable lymph nodes were palpable in the supraclavicular regions, the largest being in the left. A low grade daily fever was present. Laboratory data showed 5.1 million red cells and 8,500 white cells. Other routine examinations were noncontributory. Two sputum examinations by the concentrate method were negative for tubercle bacilli. The tuberculin test (1:1000), as well as the histoplasmin skin test, was negative. Roentgen examination showed a circumscribed mass in the right hilar region with a light infiltration in the midlung field (figure 3). The mass measured 5 x 3 cm. The left lung was clear. Fluoroscopy yielded no additional information except for visualization of a normally functioning diaphragm. Bronchoscopic examination revealed a distortion of the right bronchial tree so that the right upper lobe bronchus could not be seen. An extrinsic mass with pressure on the main stem bronchus seemed obvious. The mucosa in this area was edematous and bled easily, but no mucosal tumor was seen. The left side was normal. A supraclavicular lymph node on the left was removed and found negative for tumor specific inflammation. The findings seemed to indicate that the lesion was a malignant lymphoma, and a trial of roentgen therapy (1200 R) was given without producing any symptomatic improvement or decrease in the size of the tumor.

Operation: On August 31, 1945, through a posterolateral incision, a right exploratory thoracotomy was carried out. The sixth rib was removed subperiosteally and the pleural cavity opened. No fluid was encountered in the pleural space and the lung was not adherent to the chest wall. A mass, the size of a lemon, was palpated in the hilum of the lung. It was rock-like in consistency and so firmly fixed that removal was technically impossible. A satisfactory biopsy was taken from the mass. The chest was closed without drainage and 50,000 units of penicillin were injected into the pleural space.

Pathological report: "The section is made up of a dense, hyalinized, relatively avascular, connective tissue. In the center of this there is a small area of calcification and ossification. Diagnosis: Probably healed tuberculosis." The tissue was not stained for tubercle bacilli.

The postoperative course was uneventful and the patient was transferred to a sanatorium in the third postoperative week. At last report in November, 1945, the patient was doing well, his cough was decreasing, he had had no more hemoptyses and he was gaining weight. Roentgenograms showed the mass to have slightly decreased in size.

Comment: Although this patient was not in the cancer age, his several months' history of dry and then productive cough, the pulmonary hemorrhages and the roentgenogram strongly suggested bronchogenic or mediastinal malignancy. Because of his age and the shape and location of the mass, Hodgkin's disease received first consideration and the patient received a trial of X-ray therapy. Since no improvement resulted, an exploratory thoracotomy was indicated. Although the vocal cords and diaphragms moved normally and there was no indication of pleural fluid, the possibility of removing the lung seemed remote because of the location of the mass. This is the only case of the 4 in which the diagnosis of tuberculosis cannot be considered reasonably proved. Since tuberculosis is the commonest cause of hyalinization and calcification in lung tissue,

this must be the probable pathological diagnosis in the absence of any more specific findings.

In spite of an old, healed, apparently tuberculous mass, the pathological findings seemed to explain the patient's symptoms because of the bronchial mucosal involvement adjacent to the hilar mass. Bronchoscopy had revealed the red, easily bleeding and edematous membrane, which was the most obvious cause of the cough and hemoptyses, the two chief complaints on admission.

Case 4: F. B., a 26-year-old white male, was admitted to the University of Virginia Hospital on August 8, 1945. He had had a hacking cough for six months, but it had become productive of moderate amounts of mucoid secretions during the last two months. He also had had several small hemoptyses, a weight loss of 30 pounds, pain and wheezing in the right chest and weakness. There were vague gastro-intestinal complaints. Nine years previously he had had a small neurogenic sarcoma removed from the right flank.

Physical examination revealed fine, moist râles in the right upper chest posteriorly and anteriorly. There were no significant palpable lymph nodes. A rounded, movable mass in the right lower quadrant was presumed to be a previously diagnosed ectopic kidney. The patient was running a low grade fever. Laboratory data showed 3.7 million red cells and 9,000 white cells. The urine was normal. Nine sputum examinations by the concentrate method were negative for tubercle bacilli. Fungus cultures were negative. The intracutaneous tuberculin test was negative in concentrations of 1:10,000, 1:1,000 and 1:300. Roentgen examination showed a dense shadow with central cavitation involving the lower part of the right upper lobe and the middle lobe. The left lung was clear (figure 4). Bronchoscopy was essentially negative except for slight edema of the right main stem bronchus and the orifice of the right upper lobe.

Operation: On September 19, 1945, through a posterolateral incision, a right exploratory thoracotomy was performed. The pleural cavity was opened in the periosteal bed of the resected sixth rib. There was no pleural fluid. The right upper and middle lobes were found adherent to the chest wall. After the lung was freed, a mass, approximately 7 x 4 cm., was felt in the lower part of the upper lobe and the upper part of the middle lobe. A biopsy was taken from the mass and frozen section revealed only inflammatory tissue. The upper and middle lobes were then removed using the individual ligation technique. The five upper ribs were partially resected as an incomplete thoracoplasty and the chest was closed without drainage. Fifty thousand units of penicillin were injected into the chest daily for the first ten postoperative days and 15,000 units intramuscularly every three hours for a week, in accordance with our technique for pulmonary resection (11).

Pathological report: "The specimen consists of lung tissue apparently representing the upper and middle lobes of the right lung. In the lower portion of the upper lobe there is a large round area (8 cm.) of necrosis with central cavitation. The area is greenish-gray in color and contains diffuse small white masses, averaging 2 mm. in diameter. Sections reveal lung tissue in which there are numerous areas showing caseation. These areas are surrounded by epithelioid cells and occasional giant cells. Other sections show lung tissue with no pathological changes. Acid-fast stains of caseous areas were positive for tubercle bacilli. Diagnosis: Caseous pulmonary tuberculosis."

The postoperative course was uneventful for the first three weeks. At this time an empyema was diagnosed, believed to have been caused by tuberculosis of the bronchial stump. Since it was an infection of mixed bacterial origin, the pleural space was drained several days later. The patient was transferred to a sanatorium for further treatment. At the latest report in March, 1946, the patient was improving steadily. A thoracoplasty had been necessary to completely obliterate the mixed empyema.

Comment: Although this patient was not in the cancer age, the gradual onset of symptoms, the productive cough, the hemoptyses, the weight loss, weakness, chest pain and wheezing were suggestive of a primary malignant lesion. There was also a possibility of late metastasis from the neurogenic sarcoma which had been removed from his flank some years previously. The onset of the disease was not typical of lung abscess but it could well have represented an abscess superimposed on a malignancy. The lesion, if malignant, was felt to be probably operable. As in all doubtful cases, an exploratory operation was advised. In this case it was planned to have frozen sections made and perform a pneumonectomy if the lesion proved to be a neoplasm, and a partial resection if it were not. We did not consider the possibility of a tuberculous lesion in view of the repeated negative sputum examinations and the negative skin tests.

DISCUSSION

In the past the risk of intervention has prevented exploratory thoracotomy. Now it is justified. Hence early suspicion has become increasingly important. Delay until a definite diagnosis is made may permit an operable lesion to become inoperable either because of direct extension or distant metastasis.

In spite of modern methods, differential diagnosis is often difficult in these cases without exploration. In this series, cough, gradually becoming productive, small hemoptyses, chest pain, weight loss and weakness are all symptoms common to bronchogenic carcinoma and tuberculosis or other chronic inflammatory disease. In 3 cases of this series orthodox methods, carefully and repeatedly applied, failed to reveal tuberculosis, in spite of active lesions, both clinically and pathologically. In the fourth case pathological inactivity of the lesion makes the negative studies less surprising. The X-ray picture in all cases was suggestive of carcinoma and the bronchoscopic examinations were noncontributory.

The value of sputum examinations depends to a great extent on the ability and conscientiousness of the laboratory personnel. A report of a sputum examination negative for tubercle bacilli means little unless the previous accuracy of the technician is known. The negative examinations reported in the 4 cases were respected because of the known ability of the bacteriological technicians, the multiplicity of examinations of each patient's sputum by concentration (except in case 2), similar negative reports from a tuberculosis sanatorium in 2 of the patients and the additional evidence of negative tuberculin tests and atypical films in all 4 cases. The only tenable explanation lies in the fact that in some cases of tuberculosis it is notoriously difficult to isolate the organisms.

In exploring for possible bronchogenic carcinoma, biopsy with frozen section is useful. It must be remembered, however, that failure to obtain material from a significant portion of the diseased area may be misleading. It is generally accepted that differentiation between neoplastic and inflammatory pulmonary lesions by palpation and inspection during the exploration is at times very difficult.

Finally it should be noted that diagnostic mistakes revealed only at or after operation must be accepted if we are to make an effective attack on cancer of the lung. They can be excused only if conscientious and complete attempts at ruling

out tuberculosis have been carried out. In this connection it is also to be noted that in none of these patients was harm done by the operation and in one case a chance at surgical cure by excision of the actual lesion present was afforded.

SUMMARY

Four cases of tuberculosis simulating bronchogenic carcinoma are reported.

The difficulties of differential diagnosis are discussed.

The desirability of exploratory thoracotomy in doubtful cases is emphasized.

SUMARIO

Comunicanse cuatro casos de tuberculosis que simulaba carcinoma broncogénico.

Repásanse las dificultades que entraña el diagnóstico diferencial.

Recálcase la conveniencia de ejecutar una toracotomía exploradora en los casos dudosos.

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MITRAL STENOSIS AND PULMONARY TUBERCULOSIS¹

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Students are still taught that mitral stenosis and pulmonary tuberculosis do not occur together. White (4) reviewed the evidence and stated that the view that pulmonary tuberculosis is rare in the presence of considerable mitral stenosis appears to be true. In my experience nearly 1 per cent of patients with active pulmonary tuberculosis had mitral stenosis.

My patients with pulmonary tuberculosis have been questioned routinely for past history of rheumatic fever. Among 725 patients with active pulmonary tuberculosis and tubercle bacilli in their sputum, 27 patients gave convincing evidence of rheumatic fever, and 3 others gave a history of chorea in childhood. A history of rheumatic fever was only accepted if acute rheumatism had been diagnosed by a physician, if the age of onset was between 4 and 25 years and if the patient had had to spend at least twelve weeks in bed at the acute phase. Histories were accepted on less rigid criteria if they were supported by previous medical records, physical signs or skiagrams of the heart suggestive of rheumatic valvulitis. Of the 27 cases with evidence of rheumatic fever and tubercle bacilli in their sputum, 6 showed unequivocal signs of mitral stenosis (see table 1). In 5 of these the characteristic presystolic murmur was heard during life and, when one of these patients died, autopsy confirmed the clinical findings. The sixth patient was not known to have had mitral stenosis during life, but at autopsy presented classical rheumatic endocarditis with mitral stenosis, and phthisis. Of the remaining 21 patients, 2 more (males, aged 24 and 29) came to autopsy, but though they showed rheumatic mitral disease there was no stenosis. It is possible that other cases of mitral stenosis existed in this group but clinical proof was lacking.

TABLE 1

Six cases of mitral stenosis associated with phthisis

CASE NUMBER	SEX	AGE	AGE OF ONSET OF		REMARKS
			Rheumatic fever	Symptoms of tuberculosis	
1	F	32	11	31	Autopsy
2	M	20	No history	28	Autopsy. See text.
3	M	44	32	41	Aortic regurgitation also present.
4	F	21	7	20	
5	F	18	10	18	
6	F	28	14	27	

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During the period when these 725 patients with active tuberculosis were seen (which included the 30 cases with rheumatic fever or chorea), I saw 583 other patients with convincing histories or signs of rheumatic fever or chorea. Of these 583, 3 developed lymphocytic pleural effusions and 3 others stated that they developed active pulmonary tuberculosis from which they recovered.

SUMMARY

In several series of routine examinations of adults and school children the incidence of rheumatic heart disease was found to be approximately 1 per cent (Morris and Titmuss (1), Paul (2)). In my experience nearly 1 per cent of 725 patients with tubercle bacilli in their sputum had mitral stenosis. The incidence of rheumatic heart disease evidently exceeds that of mitral stenosis. Thus, the incidence of rheumatic heart disease in pulmonary tuberculosis would seem not to be less than that in the general population. The presence of mitral stenosis does not protect against phthisis. Roberts and Lisa (3) carefully studied the hearts of 100 patients with extensive active pulmonary tuberculosis who came to autopsy. They found healed rheumatic mitral valvulitis in 5 hearts.

SUMARIO

En varias series de exámenes sistemáticos de adultos y escolares, la incidencia de las cardiopatías reumáticas resultó ser aproximadamente de 1% (Morris y Yitmas (1), Paul (2)). En la casuística del A. casi 1% de 125 enfermos con bacilos tuberculosos en el esputo tenían estenosis mitral. La incidencia de las cardiopatías reumáticas excede manifiestamente la de la estenosis mitral, de manera que la frecuencia de las primeras en la tuberculosis pulmonar no es aparentemente menor que en la población general. La presencia de estenosis mitral no protege contra la tisis. Roberto y Lisa (3) estudiaron cuidadosamente los corazones de 100 enfermos con extensa tuberculosis pulmonar activa en quienes se hizo la autopsia, descubriendo valvulitis mitral reumática curada en cinco corazones.

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EXTRAMEDICAL SERVICES IN AN ARMY TUBERCULOSIS HOSPITAL¹

Patient and Staff Personnel Orientation in an Army Tuberculosis Hospital

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The treatment in Army hospitals of soldiers who have developed pulmonary tuberculosis during their military service poses problems which, generically at least, resemble those found in most civilian tuberculosis hospitals. Experience with tuberculous veterans both of World War I and of World War II indicates that many are remiss in remaining under medical treatment (1). This situation is a cause of concern to Public Health Officials and others interested in the welfare of veterans and the public (2).

This report will concern itself with a discussion of techniques developed in an Army hospital, specializing in the treatment of tuberculosis, to deal with the extramedical problems commonly encountered among tuberculous soldiers.

EVALUATION OF THE PROBLEM

Ultimate rehabilitation of the tuberculous patient is dependent upon the successful integration of medical treatment, social work, vocational and educational counseling and training, and an intelligent routine for making use of leisure time.

In civilian experience the period of hospitalization is generally longer than that in an Army hospital. It has been the policy of the Army to hospitalize tuberculous soldiers until a diagnosis can be established and definitive treatment instituted (3, 4). Arrangements are then made to transfer the patient to a hospital of the Veterans Administration or a civilian hospital of the patient's choice where he may receive such additional treatment as may be required. In any case a transfer is made only when movement of the patient will not prejudice his condition. Since hospitalization in an Army hospital varies from two to six months or more, a rehabilitation program must be so designed that it is integrated into this time limitation.

Another important consideration is that federal legislation makes rehabilitation of disabled soldiers a responsibility of the Veterans Administration. Until a soldier is discharged from the service, he is not eligible to receive the benefits either of Public Law 16, 78th Congress; or Public Law 346, the Servicemen's Readjustment Act of 1944, 78th Congress.

The Army Medical Department has recognized the importance of rehabilitation of sick and wounded soldiers. Physical and Educational Reconditioning Programs have been effectively developed in Army hospitals and have contributed significantly to treatment of injuries and diseases other than tuber-

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culosis. However, the usual reconditioning techniques cannot be employed in dealing with patients with active tuberculosis.

While a variety of hospital agencies including Educational Reconditioning, American Red Cross, Occupational Therapy and others were in operation at the hospital, the knowledge of the special techniques required to deal with the problem was lacking. Moreover, such work as was being performed for the benefit of the patients was not correlated either on a service level or on the level of the individual.

The patients appeared to have the characteristic resentments concerning the Army. A majority of them had been overseas for many months and were now hospitalized in a relatively inaccessible part of the country far from home. This reaction of the patients to their disease and environment and the lack of a staff of lay personnel trained in the principles of tuberculosis treatment constituted the problem which the program to be described undertook to resolve.

GENERAL PROGRAM

Following a survey of the general situation, recommendations for a program were submitted to the Chief of Medical Service and the Commanding Officer of the hospital. The primary objective of the program was to educate the patients regarding the importance of medical treatment and to start rehabilitation which might be continued under the auspices of the Veterans Administration. For this, special orientation procedures for hospital staff personnel and the patients were developed. At the outset, participation of the various hospital services was invited on a voluntary basis.

The scheme which was approved was composed of three parts: Patient Attitude Studies, Indoctrination of Hospital Staff Personnel and Orientation of Patients. A fourth part, the Experimental Project, was added later.

1. *Patient attitude studies:* Surveys of patients' attitudes and interests were conducted as part of both the general and experimental phases of the program, in order to ascertain common problems present among patients and their general reaction to the various conditions in the hospital.

The first analysis of patient attitudes was made immediately prior to the initiation of the general program in September, 1945. This study consisted of random personal interviews with the patients on the various wards. Three major problems were revealed: the desire of the patients to know more about their disease, their uncertainty about the future and their desire to be closer to home.

A study of the psychosomatic factors in tuberculosis was made independently about this time by the Medical and Neuro-Psychiatric Services (5). Among the significant personality factors revealed by this study were obsessive and compulsive drives relating to orderliness and cleanliness, independence, resentment toward authority and optimism. The study also revealed the need for an educational project for the patient. It was recommended that this be developed as a psychotherapeutic measure to permit the patients to express their aggressive drives by constructive planning for the future.

A group of 131 patients was next studied to elicit more particular information concerning their attitudes and interests.⁴ At this time the patient census in the tuberculosis section of the hospital averaged 800 patients.

Of the 131 patients, the data pertaining to 39 were eliminated because of incomplete data, undiagnosed disease, or disease other than active pulmonary tuberculosis. Analysis of the information obtained from the remaining 92 patients revealed two significant factors: first, the critical need of these patients for medical and vocational orientation; second, age distribution and educational background would make a vocational training program desirable and feasible.

Patients were studied in five wards, one of which was composed of officer patients.

(a) *Age:* The bulk of the patients were young men. Of the 92 patients included in the study, 60 individuals (65 per cent) were in the age group of 20 to 29 years. Of the 68 enlisted patients, 48 men (70 per cent) were between 20 and 30 years. Among the 24 officer patients, 12 (50 per cent) were between 20 and 29 years.

(b) *Educational level:* Seventy-six patients (83 per cent) had completed grade school. This figure included 52 (81 per cent) of the enlisted men and all officers. Of significance, too, is the fact that 31 men (27 per cent) had either started or finished college education.

(c) *Classification of disease:* Sixty patients (65 per cent) had minimal tuberculosis, 17 (19 per cent) moderately advanced and 15 (16 per cent) far advanced disease.

(d) *Length of stay:* Forty patients (43 per cent) had been at this hospital longer than four months with the maximum length of stay that of one patient who had been hospitalized thirteen months.

(e) *Marital status and dependency:* Fifty-three patients (58 per cent) were single, 35 (38 per cent) were married, 3 were divorced and one was widowed. Among the unmarried patients, 20 (38 per cent) had from one to three dependents. Of the married patients, all had from one to four dependents.

(f) *Orientation requirements:* The questionnaire employed in this study included queries concerning a variety of factors related to vocational experience and plans for the future. For example, data were obtained pertaining to principal and secondary civilian occupation prior to military service; principal and secondary assignment during military service; and vocational plans for the future.

It was found that 31 patients (34 per cent) had no plans for the future. Of these, 22 patients, or 71 per cent, reported that they could not plan because of their medical condition. Seven (23 per cent) felt that they were unable to plan because of limited education and 8 (26 per cent) because of various personal problems.

Plans for the future were reported by 61 patients or 66 per cent of the enlisted patients and of the officer patients. Significantly, a positive correlation with previous training or experience was found for 74 per cent of the patients who reported that they had plans for the future. Among 26 per cent of the patients who reported plans for the future, no correlation could be discovered between the specified plans and the previous experience or training history; among 12 per cent of the group, the future plans reported were inconsistent with either previous experience, training or medical prognosis.

In evaluating the educational needs of the group, those patients whose reactions suggested recognition of their medical problem and its concomitant economic and social

⁴ Acknowledgment is made of the assistance given by Mrs. Beryl L. Smith of the National Tuberculosis Association, who did the major part of interviewing the patients in this study.

implications and appeared to be prepared to follow the course of treatment outlined for them were classified as requiring "routine orientation." Such routine orientation consisted of periodic consultation and guidance. Those patients who seemed unable or unwilling to accept the implications of their disease problem were classified as requiring "considerable orientation."

It was found that 60 per cent of the patients required routine medical orientation, and 40 per cent considerable medical orientation.

With regard to vocational orientation, 40 per cent appeared to require routine assistance and 55 per cent considerable orientation.

The need for social orientation did not seem to be urgent. The data revealed that routine social orientation was indicated for 90 per cent of the patients as compared to 10 per cent who were obviously in need of considerable social orientation.

(g) *Reaction of patients to medical treatment and other facilities in the hospital:* The study indicated that in general the patients were satisfied with medical care. While there were some patients in each of the wards who reported dissatisfaction with their medical officer, the almost unanimous opinion in most of the wards was that the ward officers were doing everything possible for the patients. However, in two wards a number of the patients reported dissatisfaction with their medical officers. Further investigation of this reaction indicated that the opinion of these patients was influenced by the personalities of the officers rather than by an understanding of their professional ability.

There was considerable criticism of the food served in the wards, mainly in regard to preparation and serving rather than with quality. Investigation indicated that a minimum of complaints or none at all were made by the ambulatory patients who ate their meals in the hospital mess halls in which the food was prepared in the same kitchens. The fault was found to lie partially with the unappetizing manner in which the food was being served in the wards. Frequently, it was cold by the time it reached the patients. Corrective measures easily eliminated this complaint. Loss of appetite characteristic of the disease also colored the opinions of a number of patients.

The problem of diversional activities was also commented on. Many patients felt that there should be more than two motion picture shows per week in the wards. However, from both an administrative and professional standpoint it was felt that this attitude could not be accepted.

Whereas the studies to this point were concerned mainly with eliciting general information, it was felt that there was a need for a more critical study of the factors contributing to the general problem. To study these more quantitatively, surveys of patients were subsequently included in the experimental phase.

2. *Staff indoctrination:* Study of patients' attitudes and interests as well as an analysis of the administrative procedures of the hospital indicated that hospital personnel required indoctrination on how to deal with tuberculous patients. A lecture series was therefore developed to outline the methods for dealing with the special problems of tuberculous patients. Lectures included the following subjects:

- (a) Problems of the tuberculous patient.
- (b) Pathogenesis and treatment of tuberculosis.
- (c) Psychology of tuberculous patients.
- (d) Nursing problems in tuberculosis.
- (e) Nutrition problems in tuberculosis.
- (f) Occupational therapy for tuberculous patients.
- (g) The Red Cross program for tuberculous patients in an Army hospital.

These lectures were presented each week to personnel selected from the various services and departments of the hospital.

A second medium for indoctrination of hospital staff was a Tuberculosis Advisory Council. This group was made up of the chiefs of the various services and departments of the hospital or their designated representatives. Meetings of the Council were held twice each month. At these sessions, the various problems were considered, procedures evaluated and program modifications made.

3. *Patient orientation:* The patient orientation program was composed of educational as well as diversional features. Since the various programs had to reach patients on strict bed-rest and some patients permitted only limited activity, it was imperative that the patient's bedside and the ward be the focus of all the program features. Conferences with individual patients, lectures and discussions which were presented to the patient group in each ward, educational motion picture films, pamphlets, the hospital radio and public address system and newspaper were employed as the media for presenting information to the patients.

The various parts of the program were coordinated by an officer assigned to the Medical Service. This centralized control of the extramedical services made it possible to have a continuous sequence of lectures and discussions in the wards and to regulate the amount of program activity in each ward depending on the type of cases.

(a) *Medical:* Patients undergoing treatment were found on repeated observation to lack reliable information about tuberculosis. A considerable number of the men had been admitted for treatment after their disease had been revealed by the final examination prior to being separated from the service. These soldiers, for the most part, had had no recognizable symptoms and the disclosure of their disease had a profound psychological effect upon them.

The education of patients with regard to the fundamental principles of tuberculosis, the nature of the disease and methods of treatment was a responsibility of the ward medical officers. Following his arrival at the hospital each patient was given a copy of the pamphlet *What You Should Know about Tuberculosis*. Each new patient was also seen by his medical officer shortly after admission, and the essential facts regarding his condition were explained. Periodically thereafter, patients were scheduled for conferences with their medical officer at which times any significant changes or other matters relating to the course of their disease were explained.

However, because of the variation of training, interest and personality of the various officers it was natural that there would be differences in the effectiveness of this phase of patients' education.

Recognizing this, a plan was developed whereby several medical officers were selected to lecture on the medical aspects of tuberculosis in the various wards. These officers had had considerable experience with tuberculous patients and, in addition, had the ability to explain the subject in nonmedical language. Reaction of the patients was immediate and in favor of continuing this procedure.

(b) *Extramedical:* The obvious needs of most patients for information and guidance to help them develop plans for the future and deal with their immediate problems necessitated a program of extramedical orientation.

The task was essentially one of adapting the services of the various extramedical hospital agencies, such as Educational Reconditioning, Red Cross, Personal Affairs and the Library, to the particular needs of tuberculous patients. The staff orientation project helped the personnel of these agencies to better understand the problems of tuberculous patients.

The patients' education project was started with a series of lectures which were given in each ward by representatives of the agencies. The purpose of the program and the services which each agency could make available to the patients were explained. Following this, a continuous program of service was scheduled on a weekly basis.

The Educational Reconditioning Service furnished counselors who interviewed the patients regarding their educational interests. Arrangements were made for patients who were interested in taking the General Educational Development Test to obtain academic credit for qualifying experience in the military service. This test helped many patients to receive diplomas from grade and high school as well as college credit.

Vocational interests of patients were studied principally by the use of the Kuder Vocational Preference Test. Patients who took this test were counseled concerning the significance of the scores they made. Furthermore, the program served to stimulate interest in the correspondence courses available from the United States Armed Forces Institute.

The needs for social work were met by hospital case workers of the staff of the American Red Cross agency at the hospital. At the outset the number of trained workers was insufficient to meet the case load. Following recommendations made to representatives of the American Red Cross, the staff was augmented. The work performed by the hospital case workers included assistance to patients in meeting personal and family problems, assistance to patients in filing of pension claims, liaison with medical staff and other extramedical agencies and the preparation of health and welfare reports for the relatives of the patients.

The activities of the Occupational Therapy Service were considerably increased so as to provide a regular schedule of ward service to the patients. Emphasis was placed on projects which would offer controlled activity of diversional interest to bed patients, furnish graded activity for bed and ambulatory patients designed to increase work tolerance and to develop latent skills in preparation for vocational training. The ward medical officers were consulted to determine the physical limitations of the patients in order to regulate the amount of activity permitted each patient.

Problems of the patients involving pay and allowances, insurance claims, awards and decorations, and a variety of other related matters were handled by the Personal Affairs Officer, the Army Ground Forces Liaison Officer and the Army Air Forces Liaison Officer.

By ward lectures, discussions and conferences, the Veterans Administration Contact officer brought to the attention of the patients information regarding the benefits to which most of them would be entitled following discharge from the Army. Provisions of Public Law 346 and Public Law 16 were explained.

Patients were encouraged to discuss complaints and recommendations with the hospital dietitians and the Mess Officer who visited the wards regularly. Lectures on nutrition were also given in the wards. This provided both the patients and the Dietetics Service with opportunities to appreciate each other's problems and contributed materially toward improving the patients' attitude with regard to food.

The facilities of the hospital library were made available to the bed patients by frequent ward visits by the librarian. Book carts were brought to the ward on a regular schedule. Catalogues of the books in the library were distributed.

(c) *Diversional program:* Provision was made for meeting recreational needs by a

special program of ward recreation. Recognizing the limitations upon activity which the treatment of tuberculosis requires, the diversional program was planned so as to include occupational therapy projects, feature length motion pictures, USO shows and ward games which were limited to activities requiring a minimum of physical effort.

These ward activities were scheduled in the office of the program coördinator so that no ward would receive more than the indicated amount of activity. Trained Red Cross Recreation workers were responsible for providing recreational features other than occupational therapy.

EXPERIMENTAL PROGRAM

While it was suspected that there was insufficient provision for integrating the services of the various hospital agencies to the needs of individual patients, no concrete evidence was available upon which recommendations for solution could be made.

Consequently, it was decided first to investigate the value of coördinating activities and services of the various hospital agencies on the basis of individual patients and then to attempt to evaluate the effect of this procedure.

Another problem which developed during December, 1945 and January, 1946 involved a modification of the disposition policy for patients. At that time it was found that accommodations for tuberculous patients in hospitals of the Veterans Administration could not be obtained in sufficient numbers to permit the transfer of patients to the extent and frequency previously possible. This, of course, meant that patients already scheduled for Veterans Administration hospitals would have to remain at this hospital for a longer period. Following this, the census of tuberculous patients at the hospital rose to an average of 950. Therefore, as part of the experimental program, provision was also made to determine whether this development adversely affected patient morale and to develop, experimentally, program techniques to offset any deterioration in morale.

1. *Organization:* The experimental project consisted of two phases: first, development of a ward coördinator system of orientation for patients; and second, a statistical study of patients' interests and attitudes. The experimental project was started in seven wards out of a total of thirty. In addition, a like number of control wards were selected. An effort was made to have the conditions in the experimental and control wards as nearly comparable as possible.

(a) *Ward coördinator system:* Persons were selected from three hospital agencies: Occupational Therapy, American Red Cross and Separation Counseling. Each of these persons was assigned to work in one of the seven experimental wards. They were given the title Ward Coördinator and were to integrate the needs of the individual patients with the available services of the various hospital agencies.

Prior to the initiation of this system, the ward coördinators were given a series of lectures on the purpose of the program, the nature of the medical problem, the probable questions which could be expected from the patients and the results desired from the program.

The ward coördinators were to determine the group and individual problems in the wards and were to deal with them either on the basis of their knowledge of the problems or

by requesting specialized assistance of an appropriate hospital agency. The ward coordinators were also responsible for presenting the various questionnaires to the patients.

The patients' orientation program in the experimental wards was similar to that given in the control wards and the other tuberculosis wards of the hospital. The difference was the coordination of service to the individual. In addition, in the experimental wards patients were encouraged to suggest new program features or modifications of existing procedures which they believed would be of greater help or interest to them. Participation of patients was on a voluntary basis. Each man was given the choice of participating in the various activities or of being left alone.

(b) *Statistical phase:* Surveys of patient attitudes and interests were made. These studies used information obtained from attitude questionnaires, an opinion questionnaire, a biographical questionnaire and a general information questionnaire.

A time limit of one month was set for completing the various phases of the experimental project. This was done for several reasons, foremost of which was the problem of personnel which became critical as a result of the Army demobilization program. It was also felt that if the experimental project had any merit, this could be determined after a trial period of one month.

The statistical data collected generally supported the findings in the previously discussed studies.

(1) *Attitude questionnaire:* Responses of 173 patients in the control wards and 195 in the experimental wards were obtained. The patients were asked to rate their attitudes to nine questions relating essentially to morale.

Analyzing the responses, reactions of the patients were scored and classified so as to make possible comparisons among the individual wards as well as between the control and experimental wards. The questionnaire was given twice: first, just prior to the start of the project; and, a second time, at the conclusion of the project. This made it possible also to compare any differences which might reflect the influence of the experimental project.

The data collected on the first test revealed only slight variation among the mean scores computed for the experimental and control wards. On the basis of this observation it would seem that patient attitudes in the hospital were fairly consistent. Summarizing the findings, patients rated themselves as being between "neutral" and "fairly unhappy." They felt that the hospital rated between "fair" and "poor." They felt that between "a good deal" and "a fair amount" was being done for them medically; between "a good deal" and "a fair amount" was being done for them in other ways; that for the past month or two they had felt between "good" and "fair;" that at present they felt between "good" and "fair." On the average they rated their future between "good" and "fair." Their preference regarding transfer to a Veterans Administration hospital or remaining in an Army hospital ranged between "somewhat" and "don't care" and their general morale was "fair."

The data obtained from the second questionnaire revealed differences between the mean scores of each question when compared to the scores computed for the first test. In general a shift had apparently taken place both in the control and experimental wards. This shift was manifested by a drop in morale. Measuring the change quantitatively, it was found that the drop in the control wards averaged slightly more than three times that observed in the experimental wards. It could not be determined whether the results obtained in the second questionnaire represented an actual change in patients' morale or whether it was a measure of the patients' reaction to retaking a questionnaire that had previously been given. In this connection, it was observed that many patients expressed some feeling and had to be cajoled into completing the questionnaire.

Evaluating the data, it would seem that the general reaction of the patients was not at all unusual but rather normal. It is doubtful that anyone having to follow the strict regimen of treatment as is required of tuberculous patients would be happy. Nor do most people like the idea of being in a hospital. What is surprising is that the data showed the patients to be less unhappy than might have been expected. Their opinion about the medical treatment they were receiving and the other services available seemed consistent with other attitudes. It is likely that the controversy which preceded the recent reorganization of the Veterans Administration contributed to a feeling of suspicion among the men. Many were reluctant to consider further treatment in Veterans' Hospitals for this reason.

A further clue as to the actual value of the experimental project was found in evaluating the responses made to a set of questions submitted to patients on the experimental wards at the same time that the second questionnaires were given. The patients in the experimental wards were asked whether they felt that the techniques developed during the experimental project should be incorporated into the general program and continued as part of it. Eighty-three per cent of the 140 patients who responded felt that the project should be continued and incorporated into the general program. The patients were also asked whether they were personally helped by the project. Responses of 134 patients were tabulated, 61 per cent reporting that they had been helped in amounts varying from "a little" to "a good deal." Finally, they were asked whether they believed that other patients on the ward had been helped. Seventy per cent replied in the affirmative.

(2) *Opinion questionnaire:* This was concerned with eliciting the comments and ratings which patients cared to make about the various hospital services. Analysis of the data obtained revealed that the patients felt that the hospital agencies were doing a better than average job. The patients rated the services of the American Red Cross highest. Next in order were the services of Occupational Therapy, Educational Reconditioning, the Medical Staff, Personal Affairs and the Veterans Administration Contact Representative.

Comments were also made regarding food. In this connection, the general opinion was that there had been a noticeable improvement but that further improvement was desired.

It is possible that the Red Cross recreation program which included feature length motion pictures had a significant influence upon the patients which led them to rank the general Red Cross program above that of the other services.

(3) *Biographical questionnaire:* This set of questions was given to obtain data which would primarily help the ward coördinators by furnishing information basic to counseling patients.

The statistical material collected proved to be too voluminous for presentation in this report. However, it is of interest that more than half of the 115 patients who answered the questions of the biographical questionnaire indicated that they desired to prepare themselves for future vocations. Thirty-one patients wanted to take the General Educational Development Test to receive academic credit, 19 patients desired to take the Kuder Vocational Preference Test, and 29 wished to enroll in correspondence courses of the United States Armed Forces Institute. Requests for personal interviews with vocational counselors were made by 22 patients. This information is illustrative of the practical value of this questionnaire.

(4) *General information questionnaire:* This questionnaire was based primarily on the suggestions, complaints and comments which patients had made in previous inquiries. Whereas previously the questionnaires were for the most part generic, the general in-

formation questionnaire was made up of specific questions about specific things. The patients were asked to indicate their reaction by circling "yes" or "no."

The data were valuable in further evaluating the various hospital agencies. Some rather interesting reactions were revealed. For example, it was desired to find out what the patients thought about Occupational Therapy. They were asked whether they had engaged in occupational therapy projects; whether they saw the occupational therapist often enough; whether more occupational therapists were needed and whether they felt that they were receiving as much work as they desired.

Eighty-two per cent of the men reported that they were occupied with an occupational therapy project. Only 40 per cent believed that they saw the therapist often enough. The consensus of patients was that additional therapists were more urgently needed than any other class of nonmedical personnel. Furthermore, 39 per cent of all the patients indicated a desire to do more occupational therapy.

It should be pointed out that the general activity program scheduled an occupational therapist three hours per week per ward. Another factor which undoubtedly contributed to the enthusiasm of the patients for this service was the exceptional interest and devotion to duty which was characteristic of the Occupational Therapy staff at the hospital.

It is also interesting to note that in regard to the services of the American Red Cross, patients' preference was definitely in favor of the recreation staff as compared to the social work staff. This may reflect the more popular appeal of diversional activities as compared to the more limited appreciation of the rôle of the social worker.

The questionnaire also attempted to get a more quantitative evaluation of the patients' opinions regarding medical treatment and ward discipline.

The findings generally supported those obtained previously and already discussed. Eighty-two per cent of the patients felt that they saw the ward doctor often enough. Seventy-seven per cent reported that the ward doctor was personally interested in their case. Seventy-two per cent believed that their condition had been correctly diagnosed and 78 per cent felt that correct medical treatment had been prescribed for them.

Again when these reactions were analyzed by wards it was found that in some the patients generally felt that they were not receiving the attention they deserved.

With regard to ward discipline, a sizable proportion of the men expressed a desire to have their ward quieter, yet did not wish to be transferred to another ward. This attitude undoubtedly was influenced by the friendships which had developed among the patients in the various wards and a consequent reluctance to be separated from their companions.

The problem of ward discipline was generally created by a small number of recalcitrant patients in the various wards. These sometimes influenced other patients to break hospital rules and to this extent aggravated the problem.

CONCLUSIONS

The experience described in this paper, while unique because of its setting in an Army Tuberculosis Hospital, is moreover suggestive of the vast amount of work which remains to be done with the problem of education of the tuberculous patient, not alone with regards to the nature of the disease and its personal and public health implications, but also as it impinges upon his reintegration to his community environment. Basic to this problem must be acceptance of the fact that motivation of the patient cannot be predicated entirely upon the supposition that he will react to a rational presentation of facts. Rather, he must be approached through his interests in self-preservation.

Soldiers who develop tuberculosis are hospitalized and treated in an Army Hospital only until they can be transferred to a Veterans Administration Hospital or to an institution selected by the patient. For this reason and because the Veterans Administration has the legal responsibility for the medical, economic and social rehabilitation of most of these soldiers, the usual pattern of tuberculosis rehabilitation projects is not altogether applicable in the Army Tuberculosis Hospital. Instead the emphasis must be upon orientation of the patient with the object being to impress upon him the necessity for remaining under medical care until he has received the maximum benefits of treatment.

The data clearly reveal that much can be accomplished by a coordinated rehabilitation program. That the human material considered in this study is plastic is demonstrated by the preponderance of young men as well as by their educational attainments and their desire for vocational rehabilitation assistance.

Further, the experience demonstrated that the effectiveness of a program of treatment is conditional upon availability of well-trained and experienced staff personnel operating as a team.

Finally, it should be emphasized that with the Veterans Administration lies the ultimate responsibility for the formulation of a vigorous, integrated and purposeful rehabilitation program for tuberculous veterans. Without this, it is not unreasonable to anticipate again the obvious failures of the past two decades.

SUMMARY

Recognition of the problems and consequent attitudes of tuberculous patients in an Army hospital led to the development of an orientation program designed to meet their needs for information about their disease and for guidance in planning for the future.

The program consisted of four phases:

- 1: Patient attitude studies.
- 2: Indoctrination of hospital staff personnel.
- 3: Orientation of patients.
- 4: Experimental project.

Analysis of the various data indicates that much can be done for the tuberculous soldier while he is in an Army hospital. He can be helped to understand the problems associated with his disease and his consequent responsibilities.

SUMARIO

El reconocimiento de los problemas que confrontan a los tuberculosos en un hospital militar y la consiguiente actitud tomada por ellos condujo a la elaboración de una obra de orientación destinada a atender a sus necesidades de información relativa a su enfermedad y de orientación en sus planes para el futuro.

La obra comprendió cuatro fases:

- 1: Estudios de la actitud de los enfermos.
- 2: Adoctrinación del personal hospitalario.
- 3: Orientación de los enfermos.
- 4: Proyecto experimental.

El análisis de los varios datos disponibles indica que cabe hacer mucho en pro del soldado tuberculoso mientras se halla en un hospital militar, pudiendo ayudársele a comprender los problemas relacionados con su enfermedad y las obligaciones que le corresponden.

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TUBERCULOSIS AND PREGNANCY¹

EZRA BRIDGE

It is not true that pregnancy in a majority of cases has a deleterious effect on tuberculosis, neither is it true that prospective mothers with tuberculosis should be delivered by cesarean section, and it certainly is not true that all pregnancies complicated by tuberculosis should be terminated by therapeutic abortion.

What is true about the influence of pregnancy on tuberculosis cannot be shown by combining statistics from different sources. In no branch of medicine is it possible to find so many diverse opinions, each one supported by charts, figures and percentages. One author will show that mothers with tuberculosis live three times as long as unmarried women with tuberculosis. Another will prove that pregnancy is a distinct danger to married tuberculous women, and a third investigator will claim that pregnancy has no effect one way or another on a woman's tuberculosis. It would seem to be a case of "Pay your money and take your choice."

Allen K. Krause in an editorial on pregnancy and tuberculosis in the *AMERICAN REVIEW OF TUBERCULOSIS* (1935, 31, 254) puts it this way: "Whether the individual inquiry approaches the problem biologically, statistically, clinically or, say, physiologically, it is at once apparent that, with few exceptions, the usual and average study proceeds from fallacious premises, gratuitous assumptions, and almost complete lack of definition and limitation of terms; and that from so unstable a foundation it limps through a morass of slipshod data and the crudest of handling of evidence to a palpably questionable conclusion."

It would seem the problem is too complicated for simple analysis. Perhaps it will always defy solution by figures and percentages. Maybe tuberculosis in pregnancy does not change the basic reaction pattern of women to pregnancy. Maybe women who react badly to pregnancies react no differently if in addition they have tuberculosis; and, by the same token, maybe women who respond bloomingly to their pregnancies do the same if in addition they have tuberculosis.

Studies designed to clarify the problem do not inculpate shop, factory or office. Dieting as a cause cannot be blamed (women rarely starve themselves in trying to keep slender). No case can be made against insufficient clothing. Over a hundred years ago in the period of numerous petticoats and voluminous overdresses, too little clothing was even then given as a cause of so much tuberculosis. By comparison nowadays every woman should have the disease, and badly. Yet this is not so. Attempts to place the blame on smoking, late hours and strenuous sports have met without success. Even before women had the vote and before automobiles rushed hither and yon, the connection between tuberculosis and pregnancy was a problem.

Other investigations show that early marriages with child-bearing are more of a risk for tuberculous women than later marriages; that those mothers who

¹ From Iola Sanatorium, Rochester, New York.

have their children early in life have more tuberculosis than when the children come later; that mothers discovered to have tuberculosis during or after their pregnancy have a higher mortality than those who knew they had tuberculosis before they became pregnant and had adequate medical treatment. Finally, it may be stated that, if they are properly cared for, married women have no more trouble with their tuberculosis than do unmarried women.

Girls undergo a greater physiological change in becoming adults than do boys. Psychically they have greater adjustments to make; emotionally they are under greater strain particularly in the early part of their adult life. This may have some effect on the problem.

Be that as it may, experience definitely incriminates poverty, overcrowding, substandard nutrition, and poor housing as causes of high tuberculosis rates in any age and either sex.

That nature takes special care of tuberculous women during gestation has been observed for centuries. Authorities like Hippocrates, Sydenham and Rokitansky claimed that pregnancy was good for tuberculous women. This idea is not taught these days, yet all of us are impressed by the way nature seems to protect women during gestation. Many obstetricians state that a tuberculous woman rarely dies before delivery.

Given coexisting tuberculosis and pregnancy, the attitudes of the prospective parent towards the coming child need not influence the physician to any great extent. Whether a child is wanted or not is hardly the immediate concern of the physician. Most prospective mothers with tuberculosis fear that the ordeal will adversely affect their own disease, and that the infant will be born with tuberculosis.

If the pregnancy is the third one, parents should be advised to have no more children no matter what is the condition of the mother's tuberculosis. More than three pregnancies are not well borne even if the tuberculosis has been inactive for some time. Three are enough and more than three are too many.

When pregnancy becomes a reality, the mother's present and future health is of paramount importance, the father needs further educating regarding his wife's disease, and the baby deserves special consideration.

The baby will be born free of tuberculosis with a negative tuberculin reaction. It will have to be bottle fed, will be without its mother for at least six months and will be subject to tuberculosis infection and disease if the mother relaxes her pulmonary hygiene. Otherwise its chances of becoming a healthy citizen are as good as that of any infant.

The prospective father, who has aided and abetted his mate in her battle against her tuberculosis and is party of the first part, has to be advised about future pregnancies, instructed regarding the infectiousness, the chronicity and the relapsing characteristic of tuberculosis. He must be made to realize that he faces a long period when he will have full responsibility for the health and care of the baby and the mother.

The prospective mother may have minimal, moderately advanced or advanced tuberculosis. This tuberculosis may be active, inactive or the activity may be

undetermined. It may be retrogressive, slowly or rapidly progressive or stationary, and it may be predominantly exudative, fibrotic or cavernous. The extent of the tuberculosis is not so important as the status of the disease process itself. Is it active or inactive?

Ideally, the tuberculosis of a prospective mother should be arrested or inactive for at least two years. Until this is so she should be strongly advised against pregnancy. But activity itself in a tuberculous lesion is not sufficient reason to interrupt a pregnancy already started.

In general a tuberculous woman who is pregnant must have the direction and advice of a phthisiologist as well as an obstetrician. Her tuberculosis should be assiduously treated. She should have pneumothorax or phrenic interruption, if indicated, for lung relaxation. If artificial pneumothorax is indicated in the midst of a pregnancy, it should be induced; if it is being given, it should be continued. Pleural adhesions should be severed, phrenic nerve should be interrupted—all if indicated. And there should be plenty of rest, but not necessarily at this stage in a sanatorium. The regimen outlined by the obstetrician should be rigidly adhered to.

What to advise in a given case can best be presented by trimesters. If the patient seeking advice is in the first trimester she should continue with it, if her tuberculosis is inactive. If active, she must be carefully watched and especially so if there are open cavities, recent changes in her chest roentgenograms, an increase in physical signs or loss of weight or strength. Tubercle bacilli in the sputum and high sedimentation rates should not prevent continuation of a pregnancy. If the tuberculosis is rapidly progressive and the patient toxemic, interruption should be advised and the tuberculosis should have special care in a sanatorium.

If seen for the first time in the second trimester (thirteenth to twenty-eighth week) with cavernous or progressive or advanced, active tuberculosis, the pregnancy should not be interfered with; the tuberculosis should be forcibly treated. Rest should be provided, preferably in a sanatorium, artificial pneumothorax or other surgery should be used if indicated and, if possible, other control measures adopted.

If seen for the first time in the third trimester with advanced, active or progressive or cavernous tuberculosis, the pregnancy should be left alone, as induced labor sacrifices the fetus and does not benefit the mother. Here the tuberculosis needs much care and attention, including sanatorium treatment, pneumothorax if indicated, frequent X-ray examinations and close obstetrical supervision. If the tuberculosis becomes fulminating and the patient's life or the viability of the fetus is threatened, the pregnancy should be terminated by section.

Cesarean section is rarely indicated because of tuberculosis. The accepted indications, such as contracted pelvis, apply with equal force in instances where tuberculosis is present. Usually a multipara will need no help from sectioning; but a primipara in whom the head persists in riding high, and whom the obstetrician thinks will have a difficult parturition, should have the benefit of this surgical aid. Section is always indicated if the life of the infant is at stake.

Complications in the second and third trimesters, such as hemoptysis, and pleural effusion, do not indicate interruption. However, toxemia and fever of tuberculosis may occasionally have a disastrous effect on the pregnancy, thereby requiring interruption to save the infant.

Gestation itself is not dangerous to tuberculous women but delivery, puerperium and lactation are.

Birth is dangerous according to the amount of pain, mental and physical strain, and loss of blood. Birth should be under local and/or general anesthesia. Protracted dystocia must be avoided.

General anesthesia may be used with episiotomy. Ether should be avoided if possible; however, ether well administered for a short period is usually well borne. Ether badly administered may cause an irritative bronchitis. There are no contraindications to whatever analgesic or other drugs the obstetrician wishes to use, except heavy doses of morphine and atropine. Caudal anesthesia may be used if desired.

The puerperium (from end of labor to complete involution of uterus) is the dangerous period. Here the patient should be kept in bed, preferably in a sanatorium. After three weeks she may be allowed more exercise. She should have frequent chest films and special supervision by a phthisiologist. She should not nurse the infant and should not take care of it for the first half-year. She should be constantly cautioned in pulmonary hygiene.

After-care in the months to come should be directed toward her tuberculosis. Rest, adequate diet, attention to complications and frequent X-ray examinations are indicated. If asked for, advice on avoiding future pregnancies should be given.

In considering sterilization, the wishes of the wife and husband should have weight. It should be advised after the third child. It may be approved after the first or second birth when the tuberculosis is advanced, progressive or cavernous. Therapeutic interruption in the first trimester because of the severe fulminating character and the extent of the disease may be accompanied by sterilization. It should be remembered that sterilization is not a cure-all and that the mental and physical after-effects are hard to take.

A study of discharged women at Iola Sanatorium between the ages of 5 and 40 during the ten years from 1930 to 1939 showed that 97 had 152 children. At the time of their pregnancy, 9 had primary tuberculosis, 31 minimal reinfection tuberculosis, 25 moderately advanced and 22 far advanced pulmonary tuberculosis; 10 had other forms of the disease. When delivered, 55 were active and 102 inactive.

A follow-up in 1945 showed that 10 of these 97 have active tuberculosis (7 at home and 3 in the Sanatorium) and 6 have died. These figures compare favorably with results in women who have never had children.

SUMMARY

In this article an attempt has been made to show that tuberculous mothers may have children without much danger to themselves. Attitudes on therapeu-

tic abortion, cesarean section and sterilization are outlined. Details regarding care during gestation, delivery and puerperium are given.

SUMARIO

En este trabajo se ha tratado de demostrar que las madres tuberculosas pueden tener hijos sin mayor peligro para ellas. Bosquójase la actitud tomada acerca del aborto terapéutico, la cesárea y la esterilización. También se ofrecen pormenores acerca de la asistencia que debe suministrarse durante la gestación, el parto y el puerperio.

NOTICE

Annual Meeting of the American Public Health Association October 6 to 10, 1947

The American Public Health Association announces its 75th annual meeting as taking place in Atlantic City, New Jersey, October 6 to 10, inclusive, 1947. Helping the Association to celebrate its 75th annual meeting will be the following organizations:

American School Health Association
Association of Maternal and Child Health Directors
Association of Reserve Officers of the U. S. Public
Health Service
Association of State and Territorial Health Officers
Conference of Municipal Public Health Engineers
Conference of Professors of Preventive Medicine
Conference of State and Provincial Public Health
Laboratory Directors
Conference of State Directors of Health Education
Conference of State Directors of Public Health Nursing
Conference of State Sanitary Engineers
National Committee of Health Council Executives
Public Health Cancer Association

Exhibits and the scientific program will point up progress in public health over a seventy-five-year span.

VETERANS HOSPITALS

A Survey That Brought Results

The New York Academy of Medicine Study of Veterans Hospitals for Tuberculosis

E. H. L. CORWIN¹

Cognizant of the fact that after World War I one out of every 42 veterans of the military service of the United States suffered from tuberculosis to a compensable or pensionable degree, and that the service provided by the Veterans Administration was not very satisfactory, the Committee on Public Health Relations of The New York Academy of Medicine, in coöperation with the New York Tuberculosis and Health Association, carried out in 1945, under the guidance of Dr. H. McLeod Riggins, a study of the tuberculosis facilities of the Veterans Administration, with especial reference to those in New York State.

With the consent of General Frank T. Hines, then Administrator of Veterans' Affairs, a searching survey of two hospitals—one at Sunmount and the other at Castle Point, New York—was made by Dr. David Reisner as the investigator for the Committee. It was thought imperative to make such a study, in view of the expectation that large numbers of tuberculous veterans would be discharged from the armed forces of World War II. Up to January, 1945, 13,000 such veterans had been admitted to the Veterans Administration tuberculosis hospitals, of which number 17 per cent were readmissions. At the time the study was started, between 400 and 450 new patients were being admitted each month to the Veterans Hospitals.

It was also thought that the X-raying of the armed forces at the time of demobilization would add greatly to this number, since it has been estimated that from 0.3 per cent to 0.5 per cent of the total demobilized personnel would be found to have clinically significant lesions.² Moreover, premature return to work on the part of the veterans might result in relapses and add to the state demands on hospital facilities. It was estimated at the time that we might need to provide for about one-half a million new cases.

The study dealt with the location of the hospitals planned, medical and surgical care, administrative personnel, organization of the medical staff, vocational rehabilitation, social service, follow-up of discharged veterans and the causes of dissatisfaction among the patients. In addition to the intensive study of the two hospitals in New York State, the Committee had the advice and guidance of the following men among others who appeared at their weekly meetings: Dr. James Alexander Miller, Consulting Physician on Tuberculosis, Bellevue Hospital; Dr. J. Burns Amberson, Physician in Chief, Tuberculosis Division, Bellevue Hospital; Dr. Kendall Emerson, Managing Director, National Tuberculosis Association; Dr. Edward S. Godfrey, Commissioner of Health for New York State; Dr. Robert E. Plunkett, General Superintendent of Tuberculosis Hospitals,

¹ Executive Secretary, Committee on Public Health Relations, The New York Academy of Medicine, 2 East 103rd Street, New York 29, New York.

² Scattered figures, now available, would indicate that this estimate was too high and that the actual prevalence of active pulmonary tuberculosis in discharged soldiers is probably less than one in a thousand. [Editor]

New York State Department of Health; Dr. Herbert R. Edwards, Chief, Division of Tuberculosis, New York City Department of Health; Dr. Herman E. Hilleboe, then Chief, Tuberculosis Division, U. S. Public Health Service; Colonel Roy A. Wolford, Assistant Medical Director in Charge of Tuberculosis, Veterans Administration; Dr. C. W. Lester, Consulting Thoracic Surgeon, Veterans Administration Hospital, Castle Point, New York; Mr. Godias J. Drolet, Statistician, New York Tuberculosis and Health Association; and Mr. Homer Folks, Secretary, State Charities Aid Association.

The study revealed numerous inadequacies as regards service, administration and approach.

In view of a change in the Veterans Administration at the time when the report was completed, it was thought best to withhold publication temporarily. It was, however, submitted to General Bradley and General Hawley. Although many changes recommended in the report have been made with a thoroughness and rapidity which a year and a half ago would have seemed utopian, it may be of value to record the recommendations made by the Committee in July, 1945.

RECOMMENDATIONS

Recommendations with regard to social policy concerning the patient: The Joint Committee of the Committee on Public Health Relations of The New York Academy of Medicine and the New York Tuberculosis and Health Association recommended:

- (1) That through a concerted effort on the part of the Veterans Administration, as well as the medical, nursing, social service, and rehabilitation staffs of the local hospital, the veteran and his family be educated as to the values to be gained by him and his family if he remains in the hospital until he is medically discharged. This is particularly important because a large proportion of the young veterans are in the early stage of the disease when the prospect for cure is best.
- (2) That the Administration make an effort to place the tuberculous veteran in a hospital nearest his home which provides adequate care for his particular condition. Such a plan has the obvious advantage of treating the disabled veteran near his family and where he can keep in touch with his civilian interests.
- (3) That veterans of World War I and World War II be properly segregated.
- (4) That, in view of the fact that the question of disability compensation permeates the entire problem of management of the tuberculous from both the rehabilitation and public health points of view, effort be made to remedy the situation. Possibly the law should be amended to decrease the grants for home care of veterans with communicable tuberculosis who refuse hospitalization in either a Veterans Administration facility or in a suitable hospital under other auspices.

Recommendations with regard to facilities: Since the number, standards and practices of present Veterans Administration facilities are inadequate and additional provision for the World War II veteran is required, the Committee recommended:

- (1) That the new tuberculous veteran be placed in a state or local sanatorium of recognized standing nearest his home at government expense.
- (2) That, if this plan is not feasible in all instances, new facilities be provided in suitable locations near centres of medical activity where affiliation, consultation and exchange of training personnel can easily be arranged.
- (3) That the existing Veterans Administration tuberculosis facilities be completely reorganized along recognized patterns of effective service.

Recommendations with regard to medical staff:

- (1) That the medical personnel of the Veterans Administration tuberculosis facilities be set up on a corps basis, similar to that of the United States Public Health Service, and that the clinical work of the medical staff be separated from compensation and pension work and related problems, the latter to be taken care of by nonmedical personnel.
- (2) That the requirements and provisions for appointments, salary, tenure of office, promotion and retirement of the medical staff, be taken out of civil service and placed under a system similar to that of the United States Public Health Service.
- (3) That, if it is not possible to inaugurate the corps plan, the medical personnel be organized under a Chief Medical Officer of eminence and of proved administrative ability who shall rank as an associate administrator and report only to the Administrator; and that the Chief Medical Officer be in full charge of all medical and professional services, and also be responsible for the medical policies of the Administrator.
- (4) That the Veterans Administration set up an active medical advisory board of civilian physicians to advise the national Veterans Administration.
- (5) That inducements to take up the medical work in the Veterans Hospitals be based on such considerations as opportunities for (a) professional achievement, (b) advancement on clinical grounds and (c) research work. The promotion and compensation of medical personnel should not depend entirely upon seniority, age or office-title. Full consideration should be given to ability, achievement and initiative. In this connection the Committee would further recommend:
- (6) That, after competent medical leadership has been established in the Veterans Hospitals and after these hospitals have been approved by the appropriate national bodies, a proper number of residencies be created in each facility.
- (7) That there be established in the Veterans Administration a definite and generous policy of graduate education under which medical officers would be given fellowships (including tuition and regular salary) for specialized instruction; and that this policy include aid and encouragement of the medical officer in qualifying under the specialty boards. The institution of such a policy would result in great and lasting benefits to the Veterans service.
- (8) That each hospital have on its staff a full-time pathologist, a neonatologist

gist and an adequately trained bronchoscopist who may be a member either of the medical or of the surgical staff.

- (9) That the entire medical staff be reorganized so that the clinical director can carry out the recognized duties of this office and not be burdened by quasi-medical work; that the remaining members of the staff assume their duties and responsibilities in accordance with their titles; and that the paper work of the medical staff be assumed by a well-trained administrative staff.
- (10) That the differentiation of duties of the members of the staff not be carried to the extent that only one of the staff is responsible for the pneumothorax work. It should be part of the work of every ward physician.
- (11) That New York State have at least one adequate thoracic surgical centre in one of the Veterans facilities where patients from other hospitals may be transferred for major surgery. The Committee believes that in the next ten years the surgical treatment will be further emphasized but that only one centre should be organized now. The centre should have a competent full-time surgical staff with well trained assistants and an outstanding civilian medical consultant. It would be desirable if the thoracic surgeon were certified by the American Board of Surgery.
- (12) That clinical records of all veterans be made available according to a district or a state plan.
- (13) That outpatient departments be established by the Veterans Administration in coöperation with local health departments and local tuberculosis hospitals in the various parts of the country for the purpose of follow-up work and supervision of veterans, with particular attention to those who still have the disease in a communicable stage.
- (14) That vocational, recreational and rehabilitative services be instituted in all Veterans facilities.
- (15) That a comprehensive plan for medical social service be organized to humanize the institutions and to effect friendly relations between the hospital and the patient and the patient's family.
- (16) That the work of the social service of the local hospital be integrated with the general organization of the Veterans Administration, whereby all the local welfare and health agencies, including the local Red Cross and local unit of the Veterans Administration, might work to a common end.
- (17) That, in relation to veterans who constitute a public health menace because of tuberculosis, the public health authorities apply the same educational and police powers that are exercised to encourage or enforce hospitalization of others in the community, similarly affected.

The membership of the Joint Committee consisted of: Drs. H. McLeod Riggins, Chairman; Albert C. Herring; Chas. Gordon Heyd; Harry S. Mustard; Max Pinner; Grant Thorburn; and E. H. L. Corwin, Secretary.

TUBERCULOSIS IN DISCHARGED SOLDIERS

WILLIAM PORTER SWISHER¹

An evaluation of the results of the first great mass X-ray survey of men inducted into the Army is now possible, since we are now in the process of reexamining them prior to their return to civilian life. In a large percentage of cases the induction film has been available for comparison with the film taken at separation. Available statistics on the discharge rate of soldiers throughout the war because of tuberculosis are known. From review of these findings we can evaluate the success of the program, determine the sources of error and perhaps suggest ways of diminishing them, and study the effect of this program on the future public health aspects of the disease.

Each soldier at the time of discharge is given a complete physical examination and an X-ray examination of the chest. If there is any questionable shadow on the film, it is repeated and the soldier is sent to the hospital for study.

From the time the separation center started until March 15, 1946, 196,000 soldiers were examined at Separation Center Number 33, Camp McCoy, Wisconsin. Of this number, 226, or 1.15 per thousand, were sent to the hospital for further study in regard to tuberculosis. No disease was found in 24 and in 20 a diagnosis of arrested tuberculosis was made; 175, or 0.88 per thousand, were diagnosed as having active tuberculosis. Rates were somewhat higher than seen in other separation centers in the Sixth Service Command. However, these low figures are in contrast to the 3 to 15 per thousand as found in the same age group on induction (2, 8, 11, 22) and the 6 per thousand found in civilian industrial surveys (7, 19). This indicates that there is considerably less tuberculosis in the Army than in the rest of the population. It is also an index of the success of the program for screening at induction by the use of chest films.

The records of the first 157 consecutive cases of tuberculosis admitted to the hospital were studied (see table 1). It was found that 73 per cent gave no evidence of tuberculosis on physical examination. Bobrowitz (1) in a similar survey found a percentage of 71 and Morse (11) in a survey of minimal tuberculosis found that 86 per cent showed no physical signs. Until 1940 a history and physical examination was the method generally used for screening out active tuberculosis.

Further study of these cases revealed that 47 per cent had minimal tuberculosis, 40 per cent were moderately advanced and 7 per cent were far advanced; 6 per cent were not classified; 10 of the far advanced cases had more than one lobe involved, including one patient with miliary tuberculosis. All patients with far advanced lesions had elevated sedimentation rates and afternoon temperatures above 99°F.

There were 62 patients with moderately advanced tuberculosis. If routine X-ray examination of the chest had been omitted 64 per cent of these moderately advanced cases would have been missed. Of the 74 minimal cases, 52, or 70

¹ 636 Church Street, Evanston, Illinois.

per cent, had neither physical findings nor a pertinent history, further emphasizing the importance of the routine X-ray films in finding minimal tuberculosis.

The location of the lesion, as shown in the flat film, was studied (see table 2). In the minimal cases the lesion was found in the same proportion in either lung. In the moderately advanced cases it was most frequently seen in the right upper lung field and the second most frequent location was the upper left lung field. The higher incidence of disease in the right upper lung field in this small series of moderately advanced cases is in keeping with the observations of others in larger series (18).

TABLE 1

Percentage of patients without symptoms or physical findings

	MINIMAL	MODERATELY ADVANCED	FAR ADVANCED	NOT CLASSIFIED	TOTAL
Without symptoms.....	87	80	46	80	80
Without physical findings.....	80	76	28	60	73
Without symptoms or physical findings.....	70	64	0	50	58

TABLE 2

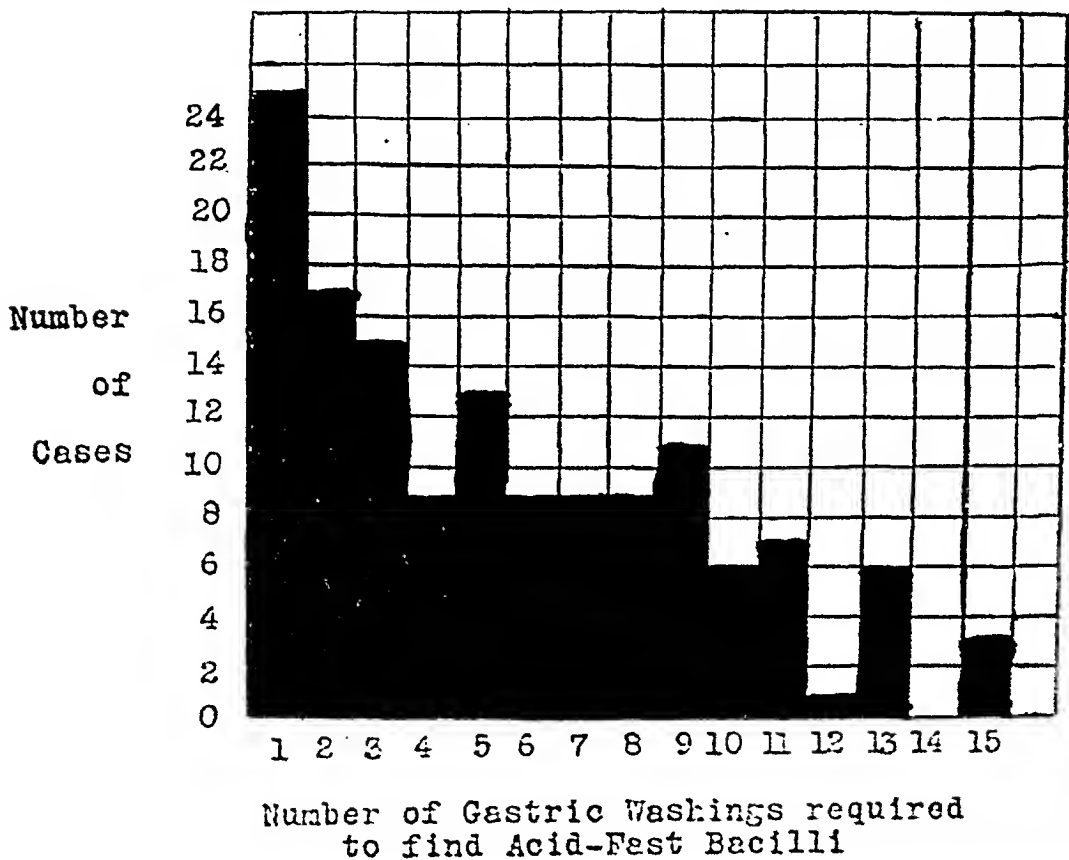
Portion of lung field involved in minimal and moderately advanced cases

	RIGHT LUNG FIELD			LEFT LUNG FIELD		
	Upper Third	Middle Third	Lower Third	Upper Third	Middle Third	Lower Third
Minimal.....	30	7	0	29	6	0
Moderately advanced...	32	5	0	25	0	0

Gastric washings were used if the patients could not readily raise sputum. Smears of the concentrates of these washings were examined daily on twelve consecutive mornings. While this may not have been the ideal method and the possibility of some false positive findings existed, facilities for injecting such a large number of guinea pigs were not available. Cultures were made in most instances if acid-fast bacilli were seen on smears. The laboratory workers were diligent and interested in the problem and contributed greatly to the success of this method of demonstrating acid-fast bacilli. If the process had been stopped after the third examination, 56 per cent of the cases would have been missed (see graph 1). When we study only the minimal cases, 32 per cent had positive smears during the first three examinations and 68 per cent would have been missed if twelve daily gastric washings had not been examined. More positive cases would have been discovered had animal inoculation been used in addition to examining the smear (4, 12, 15).

When the separation center opened, we had a number of patients in whom we could not demonstrate acid-fast bacilli in the gastric washing in spite of unequivocal X-ray evidence of pulmonary disease. This was due to some errors in the concentration technique which were eliminated in October, 1945.

There was no correlation between the character of the density as shown on X-ray films, the number of times gastric washings were examined before acid-fast bacilli were found, the sedimentation rate rise or the elevation of afternoon



GRAPH 1

temperature. This correlation was sought in an attempt to arrive at some means of determining activity with greater ease.

Induction films were available on 62 of the patients with proved active tuberculosis. Twenty-nine, or approximately one-half of these films, showed tuberculosis lesions which could be seen without difficulty. Another 12 had changes which were equivocal due either to the film technique or the nature of the lesion. Captain Stearns found that 66 out of 100 soldiers hospitalized because of tuberculosis had shadows on their induction films that should have been investigated at that time (5). It is unwise to assume from these small surveys that if every induction film had been read accurately our tuberculosis rate at separation cen-

ters would have been cut in half. On the other hand, the problem of the "missed" case on induction has been a source of concern for some time. Long and Stearns (9), in reviewing induction films, found an average of 6 cases of tuberculosis per ten thousand films studied. They listed as causes for these errors: unskilled roentgenologists, the obscuring of minimal lesions by bony structures, clerical errors and the monotony and fatigue caused by this type of work. Attempts were made to improve the roentgenological survey and to eliminate the source of error. As any procedure is only as good as the men who do the work, it seems to be a logical starting point. Extremely rapid expansion of the Army found it with an insufficient number of adequately trained men to read the films in the early days of the war. However, since many of our cases had rather obvious lesions on induction, the factor of fatigue must be considered. For example, laboratory workers in studying smears for acid-fast bacilli have been known to finish their work quickly finding all smears negative, but when a positive smear is found this stimulates interest and the technicians spend more time studying the slides resulting in more positive smears. It is the spark of interest that results in efficient work. The roentgenologist must be imbued with the importance and significance of his work in any mass studies in order to minimize errors.

Röntgenological techniques also have been stressed in the literature and their importance cannot be overemphasized. Better visualization of the lung fields leads to less fatigue to the interpreter and better end-results. The stereoscopic view plus the examination of each film separately should give optimum results (15). The 4 x 5" film, according to those who have studied comparative methods, results in a minimum of expense and a minimum of lesions missed because of the technique (6, 10, 13, 22). In our experience the induction films that were full-sized had as high a percentage of missed lesions as the smaller ones, showing that the "fatigue" element was the important factor.

Perhaps by choosing the proper type of roentgenologist for this work we can pick one who likes routine and has a definite feeling of satisfaction for exacting detail. In order to select men who have exceptional capacity for reading many films for prolonged periods of time, some test may be devised. One rather simple test to determine a man's aptitude would be occasionally to insert a certain known number of positive chest films in the daily routine. This would, after standardization, give any film reader his percentage error. It could be repeated from time to time as a check on the individual. In a short time there would be a large group of radiologists who could read a large number of X-ray films daily and the percentage of errors could be kept at a definite known level at all times.

Another suggestion to add to the preventative measures taken by the United States Army would be a method of "follow-up" in indicated cases. It is generally believed that persons with preëxisting arrested or healed tuberculosis are more susceptible to reactivation of the disease under stress, especially in the younger age group. Such persons would do well to have a chest film every three to six months, depending on their condition. Others who need closer supervision are

those who give a history of tuberculosis in the family, the case with pleurisy with effusion of unknown etiology, the patient with spontaneous pneumothorax and perhaps even the person with a negative tuberculin test (4, 20). A tuberculosis register could be instituted similar to the syphilis register in the soldier's service record. In this way the suspect would get a chest film at needed intervals. This would provide as effective a follow-up on tuberculosis suspects as it does in the syphilitic.

A central committee of qualified men would provide a standard interpretation of the films and a central clearing house for the films which would be readily available if the individual's progress indicated the need for further study in a general hospital.

The routine use of the chest X-ray film in the Army has been one of the greatest contributions to case-finding and treatment of tuberculosis in recent years and a tremendously effective public health measure. It is perhaps the forerunner of an era when everyone will have a periodic chest film, just as to-day many have periodic urinalysis and serological tests. By these means pulmonary tuberculosis will be found in the minimal stage and clinics, hospitals and sanatoria will be treating mainly minimal cases with resulting shorter periods of hospitalization and better prognosis (17, 20).

SUMMARY

A study of tuberculosis patients, as revealed by the Camp McCoy Wisconsin Separation Center Number 33, revealed that, in 196,000 soldiers, active tuberculosis was found in 0.88 per thousand; 62 per cent of these had neither a history of symptoms nor signs on physical examination that would have led to the diagnosis; 47 per cent had minimal tuberculosis; 40 per cent were moderately advanced; 7 per cent were far advanced and 6 per cent were not classified. The lesion was usually located in the upper third of the lung fields and lesions in the right upper lung field were more frequent than in the left upper lung field.

The value of repeated examinations of the gastric washings for acid-fast bacilli was evident; only 44 per cent of the cases had positive smears on the first three examinations.

Approximately one-half of the induction films available of these patients showed tuberculous lesions. These errors in reading induction films are discussed and a method of keeping them at a minimum is presented.

A method of closer follow-up is suggested by which arrested and suspicious cases would get interval chest films. The universal use of X-ray examination as a method for screening out tuberculosis opens the possibility for the elimination of the disease.

SUMARIO

Tuberculosis en Los Licenciados del Ejército

A la luz de los datos del centro de Separación No. 33 en el Campamento McCoy de Wisconsin, de 196,000 soldados separados del Ejército de E. U. A., 0.88

por ciento revelaron tuberculosis activa; en 62 por ciento de ellos no había antecedentes de síntomas o signos descubiertos por el examen físico que hubieran orientado el diagnóstico; 47 por ciento tenían tuberculosis mínima; 40 por ciento moderadamente avanzada; 7 por ciento muy avanzada; y 6 por ciento no fueron clasificados. Por lo general la lesión se hallaba en el tercio superior de los campos pulmonares, siendo más frecuentes en el lado derecho que en el izquierdo.

Resultó manifiesto el valor de los exámenes repetidos de los lavados gástricos en busca de bacilos ácidosresistentes; sólo 44 por ciento de los casos mostraron frotos positivos en los primeros tres exámenes.

Aproximadamente la mitad de las películas de entrada que había para estos enfermos revelaban lesiones tuberculosas. Discútese estos errores en la lectura de las películas de ingreso, ofreciéndose un método para reducirlos al mínimo.

Propónese un método para observación subsecuente más detenida, con el cual se harían periódicamente películas torácicas en los casos estacionados y sospechosos. El empleo universal de los exámenes roentgenológicos para despistar la tuberculosis entreabre la posibilidad de eliminar la enfermedad.

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THE QUANTITATIVE TUBERCULIN TEST^{1,2}

Its Significance in the Diagnosis of Tuberculosis

C. EUGENE WOODRUFF

Recent developments in the antituberculosis campaign have considerably increased the burden of the sanatorium laboratory. Fifteen years ago, for example, nearly all of the patients admitted to Maybury Sanatorium were either referred by another hospital or by some physician to whom the patient had gone because of symptoms. By way of contrast, the present day roster of admissions shows occasional patients picked up by a preemployment X-ray examination or in some group survey and sent to the Sanatorium solely because of a suspicious shadow in the X-ray film. Under such conditions, with an increased proportion of patients hospitalized because of X-ray findings alone instead of X-ray findings *plus symptoms*, there is a disproportionate increase in the number of cases of sarcoidosis, bronchiectasis, atypical pneumonia and lung abscess which, so to speak, have been filtered out by the X-ray screen. It is the responsibility of the laboratory to pass final judgment regarding the correctness of the diagnosis in each such case. It is because of the weight of this responsibility that the present plea is made for a more effective use of that old tool, the tuberculin test.

During the past five years, 3,381 patients, either newly admitted or re-admitted to the Wm. Maybury Sanatorium, have been tested with tuberculin. These patients varied in age from 13 to 80 years. The tests were given intracutaneously, using 0.1 ml. of a 1:10,000 dilution of OT (0.01 mg.). They were given routinely by the technologist, after she had taken the patient's blood count. The same lot of OT, diluted as needed, was used throughout the study. Old Tuberculin³ was employed rather than tuberculin PPD, first because it was more readily available and second in order that the results of this study might be more closely comparable with those of other studies in this area.

Reactions were read at the end of forty-eight hours; an area of induration or edema 5 mm. or more in diameter was considered a positive reaction. Patients negative to the first dilution were tested with 1:1000 OT and, if still negative, were retested at forty-eight-hour intervals thereafter with tuberculin ten times as concentrated. The final dilution used was 1:10 OT (10 mg.). In subsequent portions of the paper those patients who failed to react to the 1:10 dilution of tuberculin are referred to as *anergic* patients.

There was some variation in procedure with regard to the tuberculin tests over the five-year period. During the earlier years an interval of a few days to as much as two weeks elapsed after the first tuberculin test before the negative reactors were tested with more concentrated tuberculin. During the past year,

¹ Presented in part before the meeting of the Michigan Trudeau Society, Detroit, Michigan, November 7, 1946.

² From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

³ Furnished by Parke, Davis and Company, Detroit, Michigan.

on the other hand, the repeated tuberculin tests have been run immediately, in most cases, after the preceding test was read as negative.

Distribution of the total number of patients according to sensitivity to tuberculin is shown in table 1.

In a large series of patients, then, who are hospitalized either because of proved tuberculosis or because of X-ray findings suggestive of tuberculosis one may expect to find well over 90 per cent showing a positive reaction to either the 1:10,000 or the 1:1000 dilution of OT. If the tests are continued, one will find a small number of patients who fail to react to even the 1:10 dilution of tuberculin. In the present study that number was 43, or 1.3 per cent. This number compares with 2.3 per cent found negative to the 1:10 dilution of tuberculin by Musacchio (1) when he tested 1,000 patients at the Herman Kiefer Hospital in Detroit. The reason for this discrepancy is to be found in the 90 patients listed in table 1 as negative to 1:10,000 OT. Most of these 90 patients were accumulat-

TABLE 1
Distribution of patients according to tuberculin sensitivity

	NUMBER	OBSERVED	ADJUSTED
		<i>per cent</i>	<i>per cent</i>
Positive 1:10,000.....	2,699	79.8	79.8
Positive 1:1,000.....	452	13.4	14.0
Positive 1:100.....	55	1.6	1.8
Negative 1:10,000.....	90	2.7	
Negative 1:100.....	42	1.2	1.5
Negative 1:10.....	43	1.3	2.9
Total.....	3,381	100.0	100.0

ed during the first three or four years of the present study when there was considerable delay before the tests with more concentrated tuberculin were given. Undoubtedly, many of the 90 would have been found negative to the 1:10 dilution of tuberculin had their tests been run more expeditiously, for among the group were 56 patients who died before they had received any test other than the initial one.

During the past year, as already mentioned, the tests with more concentrated tuberculin have been given immediately, in most cases, after the preceding test was read as negative. Among the 758 patients tested in this manner, 22, or 2.9 per cent, have been found who failed to react to 1:10 OT. Considering these facts a reallocation of the patients listed merely as "negative to 1:10,000" would bring the total number of patients negative to 1:10 OT at least to the 2.3 per cent found by Musacchio, more probably to around 3 per cent of the total. In the column labelled "Adjusted Per Cent" such a reallocation has been attempted on the basis of our experience with the 758 patients.

The 43 anergic patients of the present study are classified according to diagnosis in table 2. Note that the fatality was 100 per cent among the 15 patients

who had pulmonary tuberculosis. All 15 were critically ill when admitted to the Sanatorium; all were dead in less than six weeks after their admission.

There were no other fatalities in the anergic group. The patient with Friedlander's pneumonia, though critically ill on admission, has improved, and should be ready for discharge soon. The patient with Pott's disease should also be ready for an early discharge. All of the remaining 26 patients have been discharged. Twenty-three were considered nontuberculous, or at least without active tuberculosis. Three of the patients with tracheobronchial lymphadenitis developed positive reactions to the 1:1000 dilution of tuberculin in less than three months after their admission to the Sanatorium. One can only speculate as to whether these 3 had primary infections when admitted, and had not yet become allergic, or whether they picked up primary infections while in the San-

TABLE 2
Anergic patients classified according to diagnosis

DIAGNOSIS	NUMBER OF CASES		PRESENT CONDITION		
	Total	Acutely ill on admission	Dead	Discharged	Active
Pulmonary tuberculosis.....	15	15	15	0	0
Tracheobronchial lymphadenitis.....	9	0	0	9	0
Atypical pneumonia.....	6	0	0	6	0
Sarcoidosis.....	6	0	0	6	0
Bronchiectasis.....	3	0	0	3	0
Pulmonary fibrosis.....	2	0	0	2	0
Pott's disease.....	1	0	0	0	1
Friedlander's pneumonia.....	1	1	0	0	1
Total.....	43	16	15	26	2

atorium. The patient with Friedlander's pneumonia became allergic with the improvement in his condition. The patient with Pott's disease also developed allergy within three months of his hospital admission.

Tubercle bacilli were found in the sputum of all 15 of the anergic patients who had pulmonary tuberculosis. In 13 instances the bacilli were present in large numbers in direct smears of the sputum. The other 2 patients, who had miliary disease, showed tubercle bacilli only when the sputum was cultured. Also, the patient with Friedlander's bacillus infection had a positive sputum culture on admission. Since then, with the improvement in his condition, he has had 2 negative sputum cultures and a guinea pig inoculation which proved to be negative. Tubercle bacilli were not recovered from any of the remaining anergic patients, in spite of a total of 171 examinations of sputum smears, 39 sputum cultures and 7 cultures of gastric washings.

VALUE OF THE TUBERCULIN TEST

A tuberculin survey made in Detroit in 1937 and 1938 (2), involving more than 100,000 tuberculin tests, revealed 31,592 reactors, but clinical tuberculosis

was found in only about 2 per cent of these reactors. Similar results have been obtained in many other American studies, including those in Minneapolis (3). Since the tuberculin test reveals such a small number of cases of clinical tuberculosis it is rarely used at present as the primary agent in a case-finding survey. However, this fact does not in the least minimize the importance of testing with tuberculin those persons who have been found by the X-ray examination to have suspicious pulmonary shadows. In this group the tuberculin test is of the greatest value as corroborative evidence for or against the diagnosis of tuberculosis. It is of particular importance in those patients who fail to show tubercle bacilli in smears of the sputum, for the results of the tuberculin test are available long before any answer can be expected from cultures of sputum or gastric contents.

In the present study, 93.2 per cent of the newly admitted patients were observed to react to either the 1:10,000 or the 1:1,000 dilution of tuberculin. If one considered only cases of minimal disease, where the diagnostic problem is frequently most difficult, the percentage of positive reactors would be well over 95.

The tuberculin testing of patients cannot be considered complete unless those who fail to react to the initial dose are tested with successively stronger concentrations of OT to determine quantitatively their level of tuberculin sensitivity. If, finally, a patient fails to react to the 1:10 dilution of tuberculin, certain rules are helpful in making a diagnosis. As was stated some years ago by Douglas (2) "...there is little evidence to indicate that persons with really active tuberculous disease of either primary or reinfection type fail to react to tuberculin, except in well known circumstances, such as during certain acute communicable diseases, terminal stages of or very acute forms of tuberculosis itself, the later weeks of pregnancy and following certain severe surgical operations. . . ." Paraphrasing this statement for the present study one may say that the person in good general condition, who has a lesion suggestive of pulmonary tuberculosis, should also show a positive reaction to 1:10,000 or 1:1,000 OT before the diagnosis is confirmed. Further, one may say that a patient anergic to tuberculin, who is not acutely ill, almost certainly does not have clinical tuberculosis.

The anergic patient with active pulmonary tuberculosis is always close to death, as was evidenced by the 100 per cent fatality of such patients in the present series. In a small series of 54 tuberculous patients (4) whose sensitivity level was determined shortly before death, 14, or 26 per cent, were found to be anergic.

If the anergic tuberculous patient is producing sputum the diagnosis should be made easy by the finding of great numbers of tubercle bacilli. A reason for the large numbers of tubercle bacilli in the sputum of the anergic patient has been suggested by Brasius (5) who found that tubercle bacilli grow not only in pulmonary cavities but throughout the lung tissues of the anergic patient. Bogen and Bennett (6) showed that the fatality rate is much higher in patients with numerous tubercle bacilli in the sputum than in those who are expectorating very few tubercle bacilli. Finally, the careful study of Funder and coworkers

(7) has indicated the higher fatality rate among tuberculous patients with a low level of sensitivity to tuberculin.

The quantitative tuberculin tests have not only aided in solving occasional bizarre diagnostic problems, but have made possible the detection of those rare errors which may creep into the reports of even the best ordered laboratory. For example, a positive sputum culture was reported in the case of a healthy *anergic* person. Because this patient was *anergic* the culture was checked immediately by animal inoculation; no disease resulted in the guinea pig. This is but one of several instances in which costly errors have been avoided or corrected because of the tuberculin test. The knowledge that tubercle bacilli are not found in the sputum of an *anergic* patient unless he is critically ill gives an effective check on the most important of all laboratory reports—that regarding the sputum.

DISCUSSION

A recent editorial in Public Health Reports (8) emphasized the need for checking X-ray findings with the tuberculin test before a definite diagnosis of tuberculosis is made. With this we can agree whole-heartedly. In the hospitalized patient with minimal or moderately advanced disease, who does not appear critically ill, the finding of either a positive tuberculin reaction or of tubercle bacilli in the sputum or gastric washings should be considered imperative before tuberculosis is diagnosed.

While agreeing to this extent with the editorial (8) one must take exception to the statement, "In the presence of a negative tuberculin test other reasons than tuberculosis must be found for suspicious shadows, even though their location or conformation be characteristic." This statement ignores the group of tuberculous patients who are *anergic* because of their extensive disease. Though small, this group is important, since it contains the patients most likely to be excreting large numbers of tubercle bacilli in the sputum.

From the experience gathered during the past five years the Clinical Staff of the Maybury Sanatorium is convinced of the diagnostic value of the quantitative tuberculin test. We believe that a tuberculin test should be given routinely to every patient when he is first admitted to the Sanatorium. Only in that way will the results be available at the time they are most needed—when initial therapeutic measures are being considered.

If the patient fails to react to the 1:10,000 dilution of tuberculin he should receive successively stronger concentrations to determine as accurately as possible his level of tuberculin sensitivity. If he proves to be *anergic* to tuberculin, the diagnosis is simplified by the use of two rules which have proved true without exception in our experience: (1) the *anergic* tuberculous patient is much more likely to have large numbers of tubercle bacilli in his sputum than is the highly allergic patient; (2) the *anergic* patient with active pulmonary tuberculosis is always acutely ill. A corollary of this last rule is that tubercle bacilli are never found in the sputum of an *anergic* patient unless he is acutely ill.

The above two rules and their corollary enable one to approach the differential

diagnosis of the anergic patient with confidence. In fact such a diagnosis can usually be made by merely answering the question, "Is the patient critically ill, or is he not?" While anergic patients with pneumococcus pneumonia may be very ill, diagnostic problems of this type rarely reach the tuberculosis sanatorium, being excluded by the characteristic X-ray picture and the other signs and symptoms. The highly allergic tuberculous patient may or may not appear ill; the anergic tuberculous patient is always very ill.

A brief experience with the carefully executed and properly interpreted quantitative tuberculin test will convince one that it is a most useful tool for the differential diagnosis of pulmonary lesions.

SUMMARY

1. The patient in relatively good general condition who is suspected of having tuberculosis should exhibit a positive tuberculin reaction in confirmation of the diagnosis.

2. In any large series of patients with roentgenograms suggestive of tuberculosis a certain number will be encountered who fail to react to tuberculin in high concentration. The differential diagnosis in such cases is simplified by the knowledge that the patient with active pulmonary tuberculosis who is anergic is always critically ill. Any anergic patient who does not appear ill is probably nontuberculous, regardless of the X-ray findings.

3. Tubercle bacilli are never found in the sputum of an anergic patient unless he is critically ill.

4. The anergic tuberculous patient is much more likely to have large numbers of tubercle bacilli in his sputum than is the highly allergic patient.

5. Routine tuberculin tests are one of the most important contributions of the laboratory to the diagnosis of tuberculosis.

SUMARIO

1. Para confirmar el diagnóstico en un enfermo en estado general relativamente bueno en que se sospecha tuberculosis, hay que obtener una reacción positiva a la tuberculina.

2. En toda serie numerosa de enfermos con radiografías indicativas de tuberculosis se encontrará cierta proporción que no reaccionan a la tuberculina a concentraciones altas. En esos casos simplifica el diagnóstico diferencial el conocimiento de que el tuberculoso pulmonar activo que es anérgico encuéntrase siempre en estado crítico. Independientemente de los hallazgos roentgenológicos, no todo paciente anérgico que no parece enfermo, es tuberculoso.

3. Jamás se encuentran bacilos tuberculosos en el esputo de un enfermo anérgico, a menos que éste se halle en estado crítico.

4. El tuberculoso anérgico es mucho más susceptible de mostrar grandes cantidades de bacilos tuberculosos en el esputo, que el enfermo muy alérgico.

5. Las comprobaciones sistemáticas con tuberculina constituyen uno de los más importantes aportes del laboratorio al diagnóstico de la tuberculosis.

Acknowledgments

Acknowledgment is made to the members of the Clinical Staff of the Maybury Sanatorium for their aid in the preparation of this paper. The technical aid of Mrs. Mary M. Cooke, Mrs. Ruby G. Kelly and Miss Cecile Marshall is especially appreciated.

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TUBERCULIN PATCH TEST¹

A Screening Procedure to Discover Tuberculin Reactors in Children

IRWIN S. NEIMAN AND ERHARDT LOEWINSOHN

In 1941 (1) one of us compared the relative efficiency of the tuberculin patch test and the Mantoux test. At that time it was reported that in presumably healthy children, whose tuberculin sensitivity was known, there was an agreement of approximately 95 per cent. In that study the Mantoux test was carried out with dilutions of OT and no reaction was considered final unless a test was done with at least 1 mg. of OT if higher dilutions did not produce a reaction. It was further indicated in this report that in no case where the patch test was definitely positive, was the Mantoux test negative. As a direct result of this study it has been the practice in our Clinic to use the patch test as a first test and to do Mantoux tests only when the patch test was negative or questionable but had previously been positive.

Recently the opportunity presented itself of using the patch test as a screening procedure in a previously untested group of Negro children ranging in age from infancy to 18 years. This study was undertaken to determine negative reactors who would be eligible for BCG vaccination. No information was sought as to the previous tuberculin reactivity of the persons concerned in the study. Furthermore, the work was carried out under field conditions of operation; that is, mass testing with reading schedules to be kept at definite times.

The routine consisted in applying the patch (commercially obtained) to the skin in the interscapular region previously cleansed with acetone and sometimes with alcohol. The patches were applied by field nurses. Instructions were given to remove the patch in forty-eight hours and to report back for reading forty-eight hours after removing the patch. The areas of reaction were measured and the number of papules were recorded as few, moderate or many. Roughly, our readings corresponded to the gradient stated by Furecolow and Robinson (2) of +, ++ and +++, respectively. Because it has been our experience that a reading of few papules or vesicles in the area of reaction is not always reliable in the light of subsequent Mantoux tests with 1 mg. of OT, it was decided not only to do Mantoux tests in this study on all negative patch reactors but also on those who gave only a weakly positive or 1+ reaction.

The Mantoux reactions were read at forty-eight hours and only those with a minimal diameter of 5 mm. of induration were considered positive. Reactions of less than this degree were considered questionable and those with no discernible reaction were called negative.

The results were as follows:

Total number of patches applied and read.....	2,229
Patch test positive	341

¹ From the Tice Clinic of the Municipal Tuberculosis Sanatorium of Chicago and the Department of Pathology and Bacteriology of the Chicago Medical School, Chicago, Illinois.

Patch test negative.....	1,382
Patch questionable*.....	296
Total number of Mantoux tests (1 mg. OT).....	1,542
Mantoux test positive.....	287
Mantoux test negative.....	1,059
Mantoux questionable**.....	196

* Questionable patch readings consisted of "few vesicles or papules in area of reaction."

** Questionable Mantoux reading consisted of an area of reaction of less than 5 mm. in diameter.

An analysis of these data reveals that on initial patch test 581 of the 2,259 children were positive. Retesting of the negative and questionable reactors to the patch test with 1 mg. of OT revealed an additional 287 reactors. This indicates an efficiency of 66.9 per cent, that is, only two-thirds of the total number of reactors were revealed by the initial patch test. On the other hand, the initial patch test was negative in 895 instances. In 164 children in whom the patch test was questionable, the Mantoux was definitely negative, indicating an efficiency of 84.5 per cent from this point of view. It should be noted that no consideration was given in this study to the possibility that the intracutaneous injection of 1 mg. of OT could give a negative reaction where the patch test was definitely positive. This fact has been abundantly confirmed in other studies (3).

DISCUSSION

The primary objective in doing tuberculin tests is to determine the presence of tuberculous infection. There have been and are in use several techniques of administration. Up to the present time, most informed opinion is agreed that the intracutaneous injection of graded doses of tuberculin has the highest degree of efficiency. However, there are secondary objectives which deserve consideration when selecting the most suitable method of tuberculin administration. If one is interested in finding only those members of the population who have most likely been exposed to infection or have active clinical disease, the report of Furcolow and Robinson (2) gives evidence that those with a high degree of reactivity only need be considered. Under certain circumstances, according to these investigators, single tests using relatively high dilutions of tuberculin or depending on 2+ and 3+ reactions to patch tests, may be considered effective for case-finding purposes.

Parenthetically, apropos this particular objective, we should like to cite a case that came to light in another study, which will be reported in detail later. In a community under observation for four years, during which annual chest roentgenograms and tuberculin tests were done, the findings in one family are of interest. The family consisted of the parents and 6 children ranging in age from infancy to 7 years, all of whom had negative chest films and tuberculin tests at first, second and third examinations. At the fourth examination 4 children had a mildly positive reaction to the patch test, one had a strongly positive reaction and one had a negative reaction. No chest films were taken at that time. At the fifth examination, the tuberculin reactions were strongly positive in all the

children and chest films revealed roentgenological findings compatible with active primary tuberculosis in 2. A third child, the youngest, had developed a tuberculoma of the brain in the region of the pons and subsequently died. The chest films of the mother and father at this time were still completely negative. Investigation of all possible contacts among neighbors and friends finally resulted in the discovery of the source of the infection in a far advanced open case of tuberculosis in the "boy-friend" of an aunt of the children who had visited with the family rather frequently during this period.

In this study we were not interested in case-finding but in determining negativity to tuberculin. The most accurate method necessitates at least two intracutaneous injections of either PPD or OT. Under the conditions of field work, the use of injections often leads to a rebellious attitude and reduces coöperation. To minimize this particular objection and yet retain accuracy of results, we have attempted to test the efficiency of replacing the first intracutaneous test with a patch test.

The results have been reported above and analysis does not speak highly for the relative efficiency of the patch test. However, on the basis of ease of administration and community coöperation, we feel that our objective has been accomplished.

CONCLUSION

In previously untested children the patch test may be used as a screening procedure to determine negativity to tuberculin.

CONCLUSION

En niños previamente no comprobados puede utilizarse la prueba del parche como procedimiento de selección para determinar la negatividad a la tuberculina.

Acknowledgments

We are exceedingly grateful for the technical assistance accorded this study by The Tuberculosis Institute of Chicago and Cook County. We are also very appreciative of the intelligent coöperation afforded us by the teaching staff of the Corlies Elementary School and High School and take this opportunity of complimenting them on the remarkably efficient arrangements which did much to facilitate our work. Great thanks are due, too, to the administrative office of The Altgeld Gardens Project and the Chicago Housing Authority for their coöperation in the necessary educational preparations.

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CELLULAR RESISTANCE TO PULMONARY TUBERCULOSIS AND PULMONARY INTRAVASCULAR PRESSURE

FERDINAND RODER¹

The thesis that a causal relationship exists between pulmonary intravascular pressure and resistance to pulmonary tuberculosis was set forth by me in a paper read before the society of physicians of Vienna on July 3, 1920 (1). Independently of it, this relationship was recently restated by William Dock (2). His and my explanations of this relation are, however, fundamentally different. It is the purpose of this paper to make this difference clear.

Observations of various facts in certain fields of biology had led me to the conclusions that the dependence of vitality or cellular resistance upon pressure is a universal principle of living matter, and that this causal relation is not based on the natural connection which exists between circulation and supply of potential energy and which is so obvious in higher animals, but on the not so obvious effect which varying pressure itself produces in the cells. I applied this view to the particular phenomenon of apical predilection for pulmonary tuberculosis and to the general phenomenon that in different places as well as in the same region (for instance in the apices) identical cells show different degrees of resistance. Both phenomena seemed explained by my view since capillary pressure must be higher at the bases of the lungs than in the region of the apices and since, due to local functional or anatomical conditions, it cannot be the same in all parts of the same region. The phenomena considered are unexplainable by the concept of some unknown chemical agent, because it is inconceivable that such an agent should be effective at one place and ineffective at another place of the same organ. I, therefore, based my theory of cellular resistance to pulmonary tuberculosis on the following facts.

Pulmonary tuberculosis is frequent in subjects with *cor pendulum* and in pulmonary stenosis; it is rare in mitral stenosis and kyphoscoliosis. In the last mentioned condition the protection is mainly dependent on the condition of the heart; tuberculosis becomes more frequent when myocardial degeneration sets in. Establishment of artificial pneumothorax causes, as direct measurements have shown, increase of pulmonary intravascular pressure. Since also the outflow of blood in the pulmonary veins is rendered more difficult by the introduction of air into the pleural cavity, capillary pressure must rise for both reasons. Examination of the collapsed lung at autopsy shows engorgement of the arteries and veins of the lung and empty capillaries. This fact together with the proved fact that the blood content of the collapsed lung is less than under normal conditions and also less than that of the other lung demonstrates how high the pressure must have been to which the lung tissue was subjected during life, since it is able to drive out the blood in both directions and to congest arteries and veins notwithstanding the diminished blood content. The increased pulmonary pressure puts an extra burden on the right chamber. If long enough continued, this leads to hypertrophy of that part of the heart.

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If hypertrophy fails to develop and dilatation is the only effect of increased pulmonary pressure on the heart, the case history often reveals that collapse therapy, too, has failed to produce its usual beneficial effect. Fibrosis, the somatic expression of higher vitality of the connective tissue and the desired aim of every tuberculosis therapy, is found in the collapsed lungs of normal animals, where there is certainly no chemical stimulus at work. It is also found in the uninvolved parts of the diseased lung and in the lungs of patients with mitral stenosis. All these conditions have in common an increase of pulmonary capillary pressure. The same constant relation is found in our long established and efficient methods of therapy: prolonged bed-rest, pneumothorax and high altitude. What they have in common is again increase of pulmonary capillary pressure. In practical application, this theory would open up new ways of therapy, which could be used either alone or in combination with established methods. I summarized my paper with the statement that the essential factor in the susceptibility of the apices to pulmonary tuberculosis is a low capillary pressure; the essential factor in protection against it and in the healing of it is the natural or artificial increase of pulmonary capillary pressure.

William Dock bases his theory on recent quantitative data (3) on the pressure in the right ventricles in man, which "have made it obvious that the effective arterial pressure in the cephalad third of the lungs is almost nil when an adult is in the erect posture. At such times the apical parts of the lungs have practically no pulmonic arterial inflow, and certainly no formation of tissue fluid or lymph." Because of the gravity effect of the blood column extending from the centre of the right ventricular cavity to the apex of the lung, which antagonizes the systolic pressure, "the pulmonic arterial pressure in the upper 5 cm. of the lung, even in systole, rarely can be more than 10 mm. Hg." "Since it requires nearly 15 mm. Hg pressure to overcome the difference in colloidal osmotic pressure between the plasma and the tissue fluid, no tissue fluid or lymph will be produced by filtration in the cephalad parts of the lungs of most adults while they are in the erect posture. Also, the flow of arterial blood will fall to zero, or at best to a small fraction of that at the lung bases." The author supplements his statements by a footnote: "It is now known that . . . mean effective pressure in the pulmonic arch is 12 to 16 mm. Hg when recumbent." From these premises he draws the incontestable inferences that during most of the waking hours removal of bacteria into the lymph nodes will be suspended, as will the removal of toxic bacterial products, their neutralization and dilution by lymph, and the supply of antibodies and blood-borne phagocytes. Confirmation of this theory is found in the frequency of tuberculosis in pulmonic stenosis, in its rarity in mitral stenosis, in the susceptibility of tall narrow-chested people, in the higher incidence of initial lesions of the right apex as contrasted with those of the left, and in the great frequency of silicotic lesions at the apex. Deficient removal of the dust particles and deficient dilution of them by lack of phagocytes and lack of lymph, respectively, explain the last mentioned phenomenon.

The premises on which Dock builds up his theory of apical localization of phthisis are listed by him as indisputable facts. They seem to me to be undeniable for the following reasons.

(1) No clear distinction is made between effective pressure causing circulation and effective pressure causing plasma filtration. This confuses the issue. If what is meant is pressure causing circulation, then the pressure is not truly represented by the mean pressure. The real measure of the kinetic energy of the blood is systolic pressure. To it has to be added the "sucking" factor of circulation, which acts in the same direction. Both together add up to at least 27 mm. Hg and both increase during each inspiration. This has been corroborated by recent experiments (4, 5) which show a great increase of blood flow and blood content of the lungs during each inspiration.

(2) If by effective mean pressure is meant the pressure which effects plasma filtration, nothing would be gained by recumbency, since the mean effective pressure in the pulmonic arch is 12 to 16 mm. Hg when recumbent and 15 mm. Hg are required to overcome the difference in colloidal osmotic pressure between the plasma and the pulmonary tissue fluid. As capillary pressure is certainly more than one millimeter lower than arterial pressure, the formation of plasma filtrate would be practically zero throughout the lungs when the subject is recumbent.

(3) Whatever is meant by effective pressure, the assumption that because of the very low blood pressure no plasma filtrate and lymph can occur in the upper third of the lung while the subject is erect is inconsistent with the fact that the lung has a double blood supply, the pulmonary artery supplying blood for oxygenation, the bronchial artery supplying blood for nutrition, that is, for formation of plasma filtrate. The pathogenesis of the hemorrhagic infarct of the lung shows what happens to any part of the lung if the formation of plasma filtrate is suspended, even for a short time, and, thus, a condition created which is claimed to exist continuously, as long as the subject is erect, in a large part of the lung. That pulmonary necrosis is produced by lack of capillary pressure as well as by lack of plasma filtrate is proved by the fact that occlusion of a pulmonary artery in a normal lung is not followed by infarction, but only in lungs in which the capillaries are overdistended by preëxisting venous congestion. In such lungs, because of the disproportion between the capacity of their circulatory bed and the blood volume, which is further reduced by hemorrhage into the alveoli, the capillary pressure must actually approach zero. The dryness of the infarcted area, as found at autopsy, demonstrates that under this condition formation of plasma filtrate actually does not occur. Nothing of this kind occurs in a normal lung when the blood supply from the pulmonary artery is suddenly cut off; this proves that, even in this extreme case of complete and permanent cessation of blood flow from the pulmonary artery, formation of plasma filtrate and lymph flow continue in the affected area by means of the auxiliary circulation provided by the bronchial arteries.

Although a wrong premise invalidates all conclusions drawn from it, the following points should be emphasized: (1) Rich (6) concluded that the marked concentration of dust at the apex is due to scar formation, which is far more common in the apices than elsewhere in the lung and that, by analogy, tubercle bacilli may be expected to settle more frequently in the apices in adults. (2) Blood-borne phagocytes disappear after a few hours, being replaced by phago-

cytic cells of local origin. (3) According to Dock's statement, one consequence of his theory, namely, minimal removal of oxygen from apical alveoli due to decreased blood flow and, therefore, the creation of an atmosphere, optimal to support the metabolism of the tubercle bacilli, "is probably not an important factor in apical localization" (2). (4) Conclusive experimental "evidence for the absence of any appreciable postural effect on the cardiac output" has been given by Grollman (7). His results show that cardiac output is constant with varying postures, that it is the same in the standing, sitting or recumbent position. In other words, the gravity effect on pulmonic arterial inflow is fully compensated in normal individuals by circulatory adjustments of the human organism. Compensation applies, of course, only to the source of blood pressure, it does not apply to local differences of capillary pressure caused by local differences of gravity.

SUMMARY

Apical localization of tuberculosis and individual cell resistance are explained by the causal relationship existing between capillary pressure and "cell vitality" or "cell resistance." This dependence of resistance to pulmonary tuberculosis upon pulmonary intravascular pressure is evidenced by various facts of pathology and clinical medicine. It is a special case of a universal principle recognizable in living nature.

The explanation of apical localization of tuberculosis, as given by William Dock, is, in my opinion, not tenable.

SUMARIO

La relación etiológica que existe entre la presión capilar y la "vitalidad celular" o "resistencia celular" explica la localización apical de la tuberculosis y la resistencia individual. Varios hechos patológicos y clínicos ponen de manifiesto esa dependencia en que se encuentra la resistencia a la tuberculosis pulmonar con respecto a la presión intravascular pulmonar, tratándose de la aplicación especial de un principio universal reconocible en la naturaleza viviente.

En opinión del A., carece de base la explicación de la localización apical de la tuberculosis, ofrecida por W. Dock.

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ATTEMPTED CAVITY CLOSURE WITH TRANSTHORACIC PLASMA INJECTION¹

H. M. MAIER AND ALBERT GUGGENHEIM

Spontaneous closure of tuberculous cavities has been known to occur for many years, but until recently the true mechanism involved was not clearly understood. Only since the investigations by Pagel (1), Coryllos (2, 3), Eloesser (4), Monaldi (5) and others, has the importance of bronchial factors been recognized in the formation as well as in the closure of cavities.

Long before obstruction and narrowing of bronchi had been assumed to be major causes of cavity closure, various substances were injected into tuberculous cavities to sterilize the cavity walls and stimulate the formation of granulation tissue. None of the substances used produced the expected results, nor did attempts to obliterate cavities by grafting of healthy tissues into the cavities prove successful.

During the past decade numerous investigators have tried to close cavities by artificial obliteration of the draining bronchi. However, permanent bronchial occlusion has not been achieved in man either by cauterization or by the introduction of occluding foreign substances (Pinner (6)). Several years ago attempts were made at the National Jewish Hospital (7) to close draining bronchi during Monaldi aspirations by cauterization of the bronchial mucosa. Neither electrocautery nor the applications of sclerosing agents produced a permanent occlusion of the bronchial lumen.

Artificial occlusion of the bronchi of residual cavities after Monaldi aspiration has been attempted by injecting various substances through the drainage catheter (5, 11). A mixture of magnesium silicate and aluminum silicate in collodion was used; later on, a mixture of charcoal and keratin dissolved in collodion. Complications such as activation of pericavitary foci, secondary infection of the cavity and infection of the transthoracic tract occurred.

In 1943, Thomas (8) published a preliminary report describing a new approach to the problem of cavity obliteration. Plasma obtained from the patient's blood was mixed with calcium chloride and injected through a Monaldi catheter into residual cavities. Bronchial occlusion could be demonstrated roentgenologically by means of contrast media added to the plasma. Filling of cavities, diminution in size and apparent closure were observed.

In April, 1946, in a personal communication, Thomas (9) stated: "As regards the follow-up of our early experiments, we have undoubted examples of blocked cavities resulting from the methods used. We tend to believe that little of the plasma remained but that we occluded by repeated irritation the draining bronchi already partially stenosed by disease."

Although the number of cases treated was relatively small, we felt that the method was safe and promised to produce at least temporary occlusion of bronchial lumina.

¹ From the National Jewish Hospital at Denver, Dr. Allan Hurst, Medical Director, and the University of Colorado School of Medicine, Denver, Colorado.

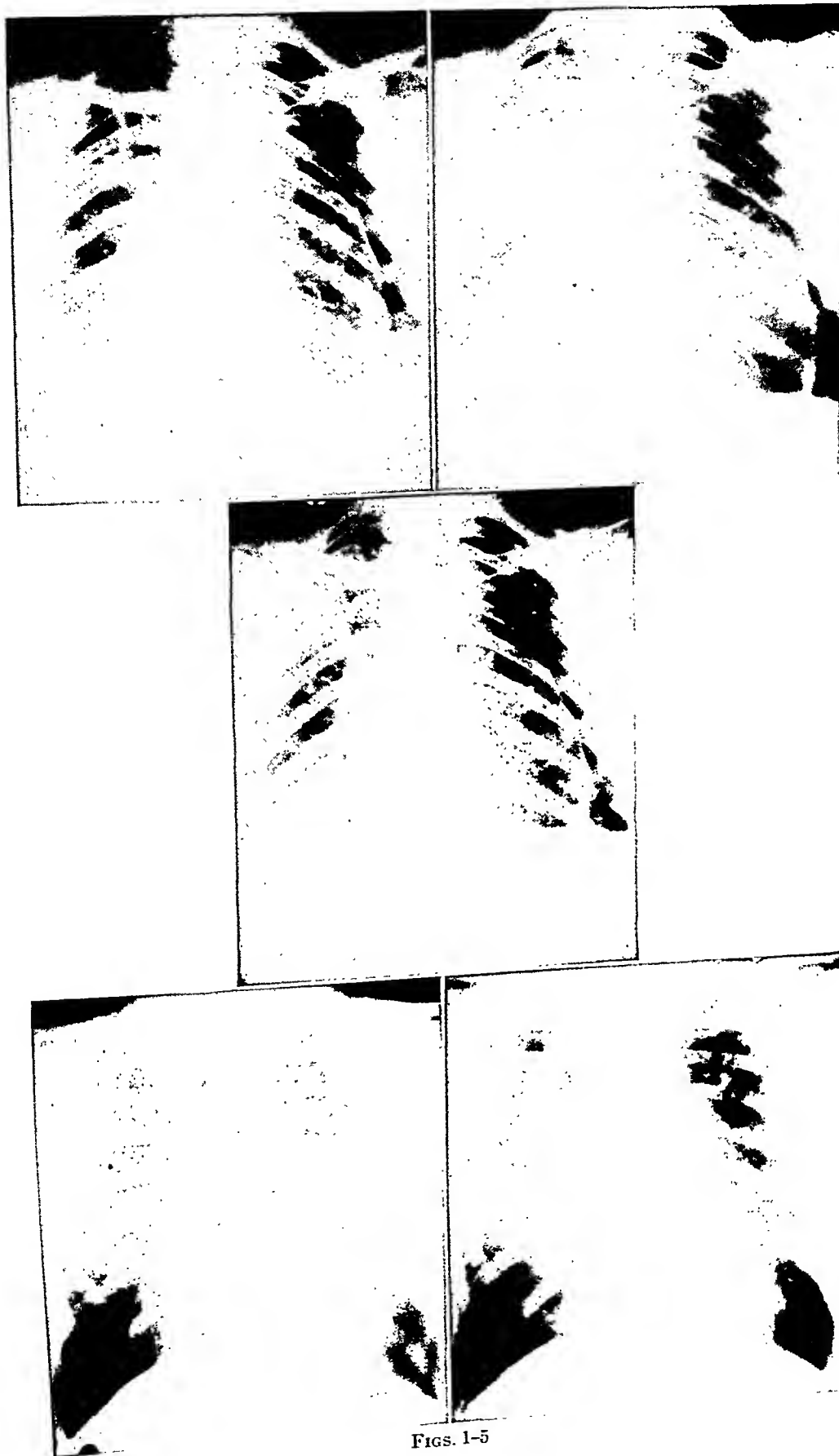
PROCEDURE

We considered at first the bronchoscopic instillation of plasma, but, because of the technical difficulties involved, we decided to inject the plasma mixture directly into the cavity by the transthoracic route. For coagulation, thromboplastin-calcium chloride was used in the same proportion as in the modified method of Quick for determination of prothrombin time (10). Plasma was obtained from the patient's blood, the prothrombin time determined, and varying amounts of the plasma, according to the size of the cavity, injected through a wide bore needle after intracavitary pressure readings were obtained under fluoroscopic guidance. The injection was timed according to the previously obtained prothrombin time so that the whole plasma mixture was injected into the cavity a few seconds before completion of the coagulation process. Before the procedure and for twenty-four hours afterwards sedative and anti-expectorant medications were given. Patients were selected with isolated cavities for which no surgical collapse procedures could be considered because of various contraindications.

CASE REPORTS

Case 1: F. W., a 33-year-old white male, with a giant cavity in the left lower lobe which had repeatedly closed and reopened in spite of phrenic interruption and pneumoperitoneum. On 1/24/46, the cavity was needled through the sixth posterior interspace in the midscapular line. Initial readings were $-12 +2$; after withdrawal of air, $-54 -38$, with return to initial pressures after a few seconds. Sixty cc. of the plasma mixture were injected. On the evening following the injection the patient's temperature was 101°F. , and he ran a febrile course, with temperature up to 103.8°F. for the following ten days. An X-ray film on the day following the procedure showed fluid retention in the cavity. Cough and expectoration were markedly diminished during the febrile period, and it was apparent that the plasma injection had resulted in a temporary cavity block with toxemie absorption. Subsequently his temperature returned to normal and serial X-ray films showed no remarkable change in the size of the cavity.

Case 2: B. D., a white male, 34 years of age, with a 4 cm. cavity in the basal axillary portion of the right upper lobe. On 1/11/46, the cavity was needled through the first anterior interspace. Cavity pressures were $-8 +2$; after withdrawal of air, $-16 -4$, returning to initial readings after a few seconds, with air being sucked into the cavity through the tracheobronchial route with an audible wheeze. These pressure readings, as in the first case, were suggestive of a weak deflationary check-valve mechanism. Twelve cc. of the plasma mixture were instilled. Following the procedure, cough and expectoration were diminished, X-ray films showed no apparent change. On 1/30/46, the cavity was needled again. Intracavitary pressures were $-12 +2$; after withdrawal of 30 cc. of air, $-24 -8$. These negative readings persisted, suggesting a reinforcement of the bronchus-cavity check-valve by the plasma instillation. Fifty cc. of the plasma mixture were again injected. On the day following the procedure, the patient's temperature went up to 101°F. X-ray examination showed an area of homogeneous density at the base of the right upper lobe. Our impression was that this represented an area of atelectasis, possibly with superimposed pneumonitis. On 2/8/46, the temperature went up to 103°F. , and the patient was somewhat dyspneic. An X-ray film showed increase of the infiltration. He was given penicillin and sulfonamide over a period of three days with lytic fall of the fever. Serial films showed progressive resolution of the infiltration, going on to complete resolu-



FIGS. 1-5

tion at the end of two weeks. The interpretation from the appearance of the serial films was that part of the plasma mixture by way of the draining bronchus had reached the segmental bronchus supplying the area below the cavity, causing a temporary occlusion with atelectasis and secondary pneumonitis. The cavity itself showed no marked change in size on subsequent fluoroscopy and films (figures 1, 2, 3).

Case 3: I. C., a 51-year-old white male, with a 4 cm. cavity in the right infraclavicular area with a well visualized draining bronchus. On 2/28/46, the cavity was needled through the fourth posterior interspace. Intracavitary pressure readings were -5 ± 4 . Air was freely withdrawn without pressure change. It appeared that the draining bronchus or bronchi were widely patent. Fifty cc. of plasma mixture were injected. An X-ray film following the injection showed a cloudy density in the cavity, representing the coagulated plasma and streaked areas of density below the cavity, probably due to plasma clots in small draining bronchi at the lower circumference of the cavity. Cough and expectoration were diminished. On 3/3/46, the cavity was needled again. The bronchial mechanism appeared unchanged with identical cavity readings. Sixty cc. of the plasma mixture were injected. Following the injection his temperature was slightly elevated for four days and the cavity appeared somewhat smaller. On 3/21/46, the cavity was needled again. Intracavitary pressure readings were -6 ± 0 . After withdrawal of 30 cc. of air, readings were $-24 - 8$, returning slowly to initial readings. This change in intracavitary pressures was evidently due to alteration of the bronchial mechanism following the second plasma injection (figures 4 and 5).

DISCUSSION AND CONCLUSION

Plasma injection in our 3 cases did not produce permanent bronchial occlusion as observed by Thomas. The slight modification in technique could not be held responsible for the failures to block the cavities. Although the cough reflex had been suppressed, it was thought that the plasma clot was coughed up with sputum after the material had been liquefied within the cavity. By subsequent intracavitary pressure readings, it could be demonstrated that the size of the bronchial lumina was at least temporarily changed but not long enough to cause a dramatic change in size or shape of the cavity. It appears that the plasma did not become adherent to the walls of the draining bronchi.

Although our initial experiments were not successful as far as the closure of cavities is concerned, it seems advisable to continue this or similar methods with different substances. Thomas later used sodium alginate and rabbit serum instead of human plasma, and found the results more satisfactory.

FIG. 1. (Upper left) Case 2. Pneumothorax left. Cavity in right infraclavicular region with recognizable draining bronchus.

FIG. 2. (Upper right) Case 2. Area of atelectasis and pneumonitis below cavity following plasma injection.

FIG. 3. (Centre) Case 2. After resolution of infiltration there is no marked change in size of the cavity.

FIG. 4. (Lower left) Case 3. Cavity in right infraclavicular region with draining bronchi.

FIG. 5. (Lower right) Case 3. After plasma injection cloudy density (probably plasma clot) is seen in lower part of cavity. Streaked areas of density below cavity are probably due to plasma clots in draining bronchi.

SUMMARY

1. Plasma—calcium-chloride-thromboplastin mixtures were injected into tuberculous cavities, using the transthoracic route. Only temporary changes in the size of the cavity as well as in the valve mechanism of the draining bronchi were observed.

2. No irreversible complications occurred. Further studies with injection of biological products appear indicated.

SUMARIO

1. Por vía transtorácica inyectáronse en cavernas pulmonares mezclas de plasma-cloruro-cálcico-tromboplastina, sin que se observaran más que alteraciones temporales en el tamaño de la caverna y en el mecanismo valvular de los bronquios de drenaje.

2. No se observaron complicaciones irreversibles. Parecen hallarse indicados estudios ulteriores con inyecciones de productos biológicos.

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RESEARCH IN TUBERCULOSIS^{1,2}

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Always down through the ages there have been those who have asked questions about the phenomena around them. They have planned schemes that would test nature's workings and answer the eternal "why." History records that man's progress has been spotty and irregular (of course from many causes) and that his advancement has been put forward mightily by great individual discoveries or efforts which have nearly always led to many subsidiary forays into the unknown.

In medicine to-day we hear much of research. But what do we mean by the term? Galdston (1) has recently advanced the interesting thought that the activities in this field may be divided into the categories of "search" and "research." He would apply the term search to efforts at the acquisition of fact and would have research mean the relating of fact to function: thus, imagination and the interpretation of fact would fit into the province of research. In this scheme the anatomical studies of Vesalius, for instance, are the product of search: those of Claude Bernard, research. Whether search or research, the world to-day is experiencing a great unfolding of fact and great expression of the "dynamic inter-relationship" of fact.

There must be a certain background to research. Facts of modern physics which made research on the atomic bomb successful have been accumulated gradually since the time of Sir Isaac Newton in the 17th century, but factual data behind the tubercle bacillus are not yet seventy years old. However, this by no means indicates that we must wait for the passage of time to do experimental and clinical study in the field of tuberculosis. It means rather that the field is large and the door is open. It means that the many unknowns in the field stand as a challenge. One prime lack of knowledge may be seen in the fact that those who have worked longest in the field are not even in agreement on the fundamental question of whether immunization against the disease should be attempted. You agree that there ought to be some sort of atomic *Blitz* which would remove tuberculosis from the world for all time; but you will agree also that more knowledge and wider use of existing knowledge are needed.

Do we need more research to-day? Tuberculosis, long the chief killer, is now in seventh place as a cause of death. New methods of diagnosis find cases early. Modern sanatoria abound, modern modes of medical and surgical treatment are in use. Many people live to-day who would have died of this disease if earlier death rates still prevailed. Some ask whether the disease is not under reasonably good control. But the fact is that it remains the chief killer, except for accidents.

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in the most productive and active ages (20 to 35). Tuberculosis is still a challenge which presents many basic problems and unknowns. We ask ourselves why people react in one way to primary infection and in another way to reinfection, but we do not have the answer. Or why the very young are prone to miliary tuberculosis and meningitis. Have we fathomed the nature of the factors which predispose to tuberculosis—that tend to convert mere infection on the one hand to clinical disease on the other? Why are we still unable to provide specific protection against this disease? When and under what conditions will we use BCG? Are we doing all we should in the revival of chemotherapy? These two latter subjects dangle most intriguing possibilities before us in tantalizing fashion, but we are still far from essential guide-lines. In the field of therapy we may wisely call for a new interpretation of rest and a new and more rational application of it. We are far from uniformity in several of the most acceptable measures of surgical treatment. In our own clinical contacts, each one of us daily feels the need of more knowledge, more wisdom.

Do we need research? Ask the man who is presented with a serious diagnostic or therapeutic problem at the bedside. Many men whose work brings them daily into contact with sick people have primary interest in the practical application of medical knowledge and are often impatient with so-called basic or fundamental research. Ideally everyone in medicine should have an absorbing interest in the unexplained phenomena before him. The question "why" should repeat itself so forcibly as to drive him to satisfy his questioning curiosity. We become research workers in proportion to the intensity of our interest, the range of our ingenuity and the depth of our understanding and wisdom. Some carry the "why" and "how" and "what" remotely in mind and find study difficult; others strive constantly to learn the answers. Thus are searches made, researches performed; thus are conditions set up to elucidate fact and to test validity of apparent fact or circumstance. Can we not, then, say properly that research is a state of mind—an attitude of life—a questioning of the hows and whys of the unknowns about us? If so, many can be researchers in spirit and in truth.

A fair amount of research in tuberculosis is currently being carried on, as the AMERICAN REVIEW and other medical journals bear witness. This is mostly done on an individual basis although some of it represents planned group-effort. The Committee on Medical Research of the National Tuberculosis Association supports a good deal of study. A word about its activities may be in order. In 1920, Gerald Webb, then President of the Association, named to a Committee on Medical Research Paul Lewis, Allen K. Krause and Wm. Charles White, the latter chairman. The Committee established its plan. It had but little money. This it wished to invest wisely. By expending small sums for technical assistance and materials the Committee could enable the research worker to utilize his skill and to use the property, equipment and overhead of the university or institution which employed him. The Committee established two general approaches: (1) correlated, coöperative research; (2) individual research.

The Committee felt that greater progress would be made under a scheme of integration and correlation than by individual effort alone. To this end, broad

subjects on which more knowledge was imperative were selected. Workers skilled in specific fields were asked to participate and thus to conduct their work under Committee sponsorship. This scheme of coördinating research had precedent. It appears that Ehrlich operated a research project in which workers applied their skills in the search for a specific chemotherapeutic agent against syphilis. These workers devised a great number of arsenical preparations which they studied pharmacologically, experimentally on animals and clinically on man before the famous 606 was produced.

The integrated investigation of the Committee stands at its best in the chemical work it has sponsored. In this work Long's synthetic medium was chosen for growing the tubercle bacillus; after growth the medium became the substance upon which Long, Seibert and fellow workers strove for the chemical purification of tuberculin. The tubercle bacilli from the cultures, in the hands of Johnson and later of Anderson, underwent chemical analysis and several chemical entities were isolated which, in turn, were studied biologically in animals by Sabin and her associates in an effort to identify fractions of the bacillus which might be responsible for symptoms of the disease.

The Committee's second approach concerned the support of research efforts of individual investigators. One of the best examples of the type of work supported in this way may be seen in William Snow Miller's anatomical studies of the lung. By providing assisting personnel, equipment and materials, the Committee made it possible for this investigator to extend greatly our knowledge of the lymphatics and blood vessels in the lungs and their relationship to the formation of tubercle, the nature of reticulum and its connection with the progression and healing of tuberculosis, and many other anatomical and pathological relationships in human pulmonary tuberculosis.

It is not the purpose of this paper to delineate items in the history of the Committee, which has been done by Nicolson (2), but rather to indicate by these few examples the general plan on which the Committee has operated since its inception. The range of its work has been relatively broad. It coöperated with the Tuberculosis Control Division of the U. S. Public Health Service and The Henry Phipps Institute in launching the now well-known study of BCG among Indians. More recently it sponsored the study of minimal lesions in conjunction with the Public Health Service.

At present there is under way a group of studies on the chemistry of the tubercle bacillus and the application of various chemical fractions of the bacillus to the animal body. A specific study is in progress on the carbohydrates of the bacillus and two on problems in respiratory physiology; two on the factors responsible for caseation and softening. Another study on histoplasmosis seeks especially to find, if possible, evidence of early infection and its rôle in causing intrathoracic calcification. Also in contemplation is the subject, among others, of sterilization of the air by germicidal lamps.

Of recent years the plea has been voiced by many for more attention to clinical problems—more study of bedside medicine—more research into the phenomena that shroud the sick man and continue to pose unanswered problems for the phy-

sician. In general medicine, research in nonclinical subjects has prospered rather better than those that are strictly clinical, and in tuberculosis this tendency has been marked. Look at the REVIEW. The editor prints all the presentable clinical material that comes to him—yet the dearth of papers on clinical investigations is obvious. Why do we not turn our attention more often to bedside medicine? Why is it that, when clinicians far outnumber those in nonclinical fields, the few among the latter submit the majority of the studies? As an example, the patient's cough offers a real problem which might be studied. There are good reasons for the patient to raise sputum. But when cough is excessive or unproductive, a dozen of us may have a dozen different approaches. But most of us will give codeine. If the cough is not controlled, we increase the dose, not knowing whether this narcotic paralyzes the action of the cilia and thus hinders the raising of sputum. We realize eventually that the cough which a quarter grain will not control is also refractory to a half or a whole grain. Why should we feel that a subject like this is simply unfathomable? Why cannot someone study cough, relate it to the type and location of disease, to posture and ease of expectoration, to ciliary action, and do the thing on a basis of scientific definition that will give us some useful answers? Or take anemia in tuberculosis which also is a relatively unexplored field, or the utilization of food by patients with different types of tuberculosis and complications. There is need for controlled scientific study of bedside problems.

The Committee on Medical Research has a schedule to keep. It is continuing its sponsorship of several of its basic studies. At the same time it recognizes the value and the desirability of attention to individual research in clinical, pathological and bacteriological domains and is prepared to underwrite such increasingly. It is well known that the Committee receives and grants requests from individuals for support of particular studies. Whoever has a study in mind will receive full consideration if he submits his problem to the Committee. To be sure the basis of the study must appear to be sound. The application must bear evidence of a well-thought-out scheme and must include a proposed budget. But the invitation is a standing one. The Committee is ready to help. Will you avail yourself of the opportunity—you who criticize the present scheme and you who do not?

Let us do more study. Let us say with the writer of Proverbs "where there is no vision the people perish." Expansion of roentgenology, of thoracic surgery, of the rationale of bed-rest, of bacteriology, physiology and pathology—all these may lead to magnificent elaboration of fact and attitude. It stands as a challenge to all of us.

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APICAL SCARS^{1,2}

Their Etiological Relationship to Tuberculous Infection

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Scars at the apex of the lung are generally regarded as healed tuberculous foci and, since they usually are bilateral, the theory has been advanced that they are lesions resulting from a postprimary hematogenous dissemination of tubercle bacilli. Rich (1) comments on this problem as follows: "Lesions of the apex are frequently found roentgenologically, but clinically, the great majority of these become permanently arrested and pathologically, they are found as the familiar, obsolete apical scars." Pinner (2) states: "Fibroid phthisis in the strict sense is healed phthisis. Dependent on the extent of the involvement, it may be represented by small, frequently apical scars of no clinical relevance . . ." Moore (3) reports an incidence of 33 per cent of apical scars in 100 white adults, considering these lesions as healed tuberculosis, and presents on page 303 a photograph of the type of lesion which will be discussed in this paper. MacCallum (4) defines these scars as follows: "Such apical lesions which are generally flat, scale-like, depressed scars over the apex of the lung, often with pigment collected about them, are extremely common in persons of middle and advanced age. They may extend into the lung substance a short way or even lie below the apex, radiating narrow lines of scar tissue into the surrounding lung and sometimes showing a caseous or calcified center. These apical scars on microscopic study rather rarely show any distinct tubercles, but there are so many transitions to a more active process that their nature cannot be doubted." To this description, the author desires to add that they vary considerably in size and shape, are predominantly bilateral with a symmetrical placement on the two sides and rarely exhibit pleural adhesions over the involved area.

During the past two years the author has been collecting, in the Medical Examiner's Department of the Borough of Manhattan, data relative to the incidence of tuberculous infection in cases of unexpected death and, as part of the study, the location and type of apical scars have been carefully recorded. Any reference to tuberculous lesions in the present discussion is on the basis of macroscopic examination which is subject to revision when a complete study, including microscopical examinations, is reported at a later date. The author is of the opinion that the completed study will not greatly alter the impressions gained from the macroscopic examination. In this investigation, cases of extensive lobular or lobar pneumonia, bronchiectasis, pulmonary tuberculosis or neoplasia, local or metastatic, were not included. These rejected cases were practically all in older persons and constituted less than 5 per cent of the material

¹ Sponsored by the Hegeman Memorial Research Fund.

² The material for this study was obtained through the courtesy of the Medical Examiner's Department of the Borough of Manhattan.

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available. Cases with unilateral or bilateral dense obliterative pleural adhesions were not investigated for apical scars. Cases with thin focal or extensive pleural adhesions were carefully studied and not infrequently typical apical scars were observed beneath the pleural adhesions. Otherwise, the only restriction was that every case be thoroughly studied, an average of two hours being required for each necropsy. The author was not responsible for the performance of the general necropsy nor for the recording of the necropsy findings in any of the cases. Persons of Caucasian and of Negro races were investigated and all cases over three months of age were included.

TABLE 1

Comparison of apical scars with age, race and presence or absence of tuberculous foci: 960 white—299 Negro

RACE	TUBERCULOSIS	APICAL SCARS	TOTAL	AGE		
				3 months to 29 years	30 to 49 years	Over 50 years
White	Present	Total	722	54	253	415
		Present	347 (48.1%)	2 (3.7%)	53 (32.8%)	262 (63.1%)
		Absent	375 (51.9%)	52 (96.3%)	170 (67.2%)	153 (36.9%)
	Absent	Total	238	82	89	67
		Present	76 (31.9%)	3 (3.8%)	28 (31.4%)	45 (67.2%)
		Absent	162 (68.1%)	79 (96.2%)	61 (68.6%)	22 (32.8%)
Negro	Present	Total	184	52	94	38
		Present	27 (14.7%)	—	14 (11.7%)	13 (34.1%)
		Absent	157 (85.3%)	52 (100%)	80 (88.3%)	25 (65.9%)
	Absent	Total	115	57	42	16
		Present	9 (8%)	1 (1.7%)	5 (11.9%)	3 (18.8%)
		Absent	106 (92%)	56 (98.3%)	37 (88.1%)	13 (81.2%)

RESULTS

Table 1 presents a comparison of apical scars with reference to age, race and the incidence of macroscopic evidence of tuberculous infection. Fourteen hundred cases were studied but 141 are not included in the data as dense unilateral or bilateral obliterative pleural adhesions, dense pleural adhesions associated with apical tuberculosis or tuberculosis of considerable extent with accompanying pleural adhesions were present. Of the remaining 1,259 cases, 960 were Caucasians and 299 were Negroes.

The relationship between age and apical scars is evident. No apical scars were found in 106 persons under 20 years of age although this group showed an incidence of 21.7 per cent of tuberculous foci. There were 140 cases between 20 and 29 years of age with an incidence of 3.5 per cent with apical scars and 59.3 per cent with tuberculous lesions. In 290 persons over 60 years of age, apical scars were present in 65.9 per cent and tuberculous foci in 88 per cent of the cases. Apical scars occurred as frequently in persons without any evidence of tuberculous lesions in their tissues as they did in those with single or multiple tuberculous foci.

It was found that apical scars occurred more frequently in Caucasians than they did in Negroes, regardless of age. A somewhat similar condition was found relative to sex in Caucasians where apical scars were present in 24.2 per cent of 219 females and in 53.1 per cent of 697 males over 20 years of age. In similar groups of Negroes, apical scars were present in 13 per cent of 85 females and in 17.7 per cent of 141 males. The incidence of tuberculous lesions in these four groups were as follows: white female, 69.2 per cent; white male, 82.4 per cent; Negro female, 61.2 per cent; Negro male, 66.7 per cent. While the white male showed the highest percentage of tuberculous infection, this fact, by itself, does not account for the difference noted in the relation of apical scars to sex and race.

Apical scars were recorded in 459 cases with a bilateral and symmetrical distribution in 446 (97.2 per cent). Nine of the 13 cases with unilateral apical scars were white males, 3 were white females and one was a Negro male who had a large syphilitic aneurysm of the arch of the aorta that protruded into the right chest with the apical scar being at the apex of the right upper lobe, perhaps a contrecoup effect. Focal adhesions were present over the apex of the opposite lung in 7 cases. The bilateral and symmetrical pattern of the apical scars bore no semblance to the asymmetrical and scattered distribution of the tuberculous lesions.

Tuberculous foci contiguous to or directly involving apical scars, which were bilateral, were observed in 33 cases with the tuberculous lesions being unilateral in 26 and bilateral in 7 instances. There were 20 persons who had apical tuberculous lesions with neither apical scars nor focal pleural adhesions. Forty-five persons, not included in the data in table 1, had tuberculous lesions with dense obliterative focal pleural adhesions in the area where apical scars usually occur with the foci being bilateral in 23 and unilateral in 22 instances, the latter group showing no apical scars on the opposite side. It is evident that tuberculous lesions can occur in the apex, unilaterally or bilaterally, with or without apical scars being present.

On occasion a lower lobe of a lung may be unusually large with its apex forming one-half or more of the dome of the lung. Twelve such specimens were observed in this study. In 6 instances, the left lower lobe occupied such a position with apical scars being present in the left lower, the left upper and the right upper lobes. One case showed the left lower lobe occupying two-thirds of the dome of the lung with apical scars present in the left lower and right upper and no scar in the left upper lobe. Another case showed the lower lobe on either side occupying

one-half of the dome of the lung with an apical scar in both lower and both upper lobes. No tuberculous foci were found in 3 of the 8 cases. In the 4 remaining specimens no apical scars were present with 3 exhibiting tuberculous foci. Another case had a large right azygos lobe with apical scars in it and in both upper lobes. Apical scars have not been observed in lower lobes except as noted above, although tuberculous foci have often been found in the upper portions of lower lobes.

DISCUSSION

The observations presented in this paper are concerned primarily with the etiological relationship between apical scars, sometimes called "apical caps," and tuberculous infection. The pathogenesis of these peculiar lesions can be determined only by a study of the process in different age groups when it may be possible to obtain specimens in different stages of development. In the present study, evidence of tuberculous infection is based on the finding of calcified or caseous foci or of tuberculous cavity in the lung parenchyma, in areas dissociated from the typical apical scar, or similar tuberculous foci in lymph nodes or other tissues. Phleboliths, small chondromata and "osteomata" have been observed in some of the cases and such lesions are fairly easily recognized from their macroscopic appearance. Flat calcified or bony plaques were frequently observed in the more superficial portion of apical scars, especially in persons over 50 years of age, and these have not been considered as indicative of tuberculous infection. Had all apical scars been interpreted as tuberculous in nature, the only effect would have been to increase, by a few percentage points, the incidence of tuberculous infection in white persons over 20 years of age. An uncritical acceptance of a tuberculous etiology for all apical scars allows a plausible explanation for the increase of these lesions with age, but the differences noted in relation to sex and race can hardly be accounted for in this manner.

The occurrence of apical scars in lower lobes only when they form half or more of the dome of the lung raises a question which cannot logically be explained on a basis of tuberculous infection. Similarly, the presence of bilateral apical scars without any definite tuberculous lesions in the rest of the tissues is not satisfactorily accounted for by the theory that such lesions are the result of a post-primary hematogenous dissemination of tubercle bacilli. Tuberculous foci do develop in the apex of the lung and they may be bilaterally disposed. They may also be found in the lung tissue contiguous to apical scars which they may involve in the course of their development. On the other hand, the bilateral symmetry of apical scars bears little semblance to the asymmetrical and scattered pattern of tuberculous lesions.

The belief that apical scars are healed tuberculous foci has long confused thought relative to the pathogenesis of phthisis. This confusion has resulted from a failure to distinguish between a strictly tuberculous involvement of the apex of the lung, tuberculous foci contiguous to apical scars and apical scars without any evidence of tuberculosis either in the scarred area or in other tissues of the body. Phthisis may have its inception in an apex and pursue an apico-

caudal course; it may begin infraclavicularly (*Frühinfiltrat*); or it may originate in the upper portions of any pulmonary lobe; and without any relation to apical scars in either instance.

Many of the apical scars noted in this study were of sufficient size and density to cast shadows on a roentgenographic film. Since significant tuberculosis may occur in the same location, it is necessary to try to differentiate between the two conditions. Fortunately, apical scars rarely occur and are always of slight extent below the age of 30 so that in the younger age groups they need not be considered, even if there are bilateral apical shadows. The increasing frequency of bilateral apical scars with advancing age indicates the necessity for caution in the interpretation of apical shadows as tuberculous, especially in white males over 50 years of age. The problem will be less complicated in Negroes for bilateral apical scars, nontuberculous in nature, are infrequent at any age in this race. Shadows of calcium density in the apical region are no sure indication of tuberculous lesions. Since tuberculous lesions in association with apical scars are more frequently unilateral than bilateral, a considerable inequality of the shadows on the two sides would suggest the presence of a tuberculous lesion.

CONCLUSIONS

1. Apical scars were observed in 423 (44.1 per cent) of 960 white persons and in 36 (12 per cent) of 299 Negroes. The incidence of tuberculous infection was 75.2 per cent and 61.2 per cent, respectively.

2. Apical scars were not observed in 106 individuals under 20 years of age. In 403 white males over 50 years of age, they were present in 275 (68.2 per cent) with the lesions being bilateral in 98 per cent. The incidence of tuberculous infection in these two groups was 21.7 per cent and 86.8 per cent, respectively.

3. In white persons over 20 years of age, apical scars were present in 24.2 per cent of 219 females and in 53.1 per cent of 697 males. Tuberculous foci were present in 69.2 per cent of the females and in 82.4 per cent of the males.

4. Apical scars were observed in lower lobes only when the apex of this lobe formed one-half or more of the dome of the lung.

5. Apical scars were present with equal frequency in persons who exhibited no macroscopic evidence of tuberculosis in their tissues and in those who had single or multiple tuberculous foci.

6. No definitive evidence was found to support the theory that bilateral apical scars represent healed tuberculous lesions following a postprimary hematogenous dissemination of bacilli.

7. It appears obvious that typical, bilateral apical scars, sometimes called "apical caps," are not etiologically related to tuberculous infection.

CONCLUSIONES

Las Cicatrices Apicales: Su Relación Etiológica con la Infección Tuberculosa

1. En 423 (44.1 por ciento) de 960 sujetos blancos y 36 (12 por ciento) de 299 negros observáronse cicatrices apicales, en tanto que la incidencia de infección tuberculosa fué de 75.2 y 61.2 por ciento, respectivamente.

2. No se observaron cicatrices apicales en 106 individuos de menos de 20 años. Entre 403 varones blancos de más de 50 años, se hallaban presentes en 275 (68.2 por ciento), siendo bilaterales en 98 por ciento. La incidencia de infección tuberculosa en esos dos grupos representó 21.7 y 86.8 por ciento, respectivamente.

3. Entre las personas blancas de más de 20 años, había cicatrices apicales en 24.2 por ciento de 219 mujeres y 53.1 por ciento de 697 hombres, en tanto que la proporción de focos tuberculosos era de 69.2 y 82.4 por ciento, respectivamente.

4. Sólo se observaron cicatrices apicales en los lóbulos inferiores cuando el vértice del lóbulo dado formaba la mitad o más de la cúpula del pulmón.

5. La frecuencia de las cicatrices apicales fué igual en las personas que no mostraban signos macroscópicos de tuberculosis en sus tejidos y en las que tenían focos tuberculosos aislados o múltiples.

6. No se encontraron datos definitivos que apoyen la teoría de que las cicatrices apicales bilaterales representen lesiones tuberculosas curadas a continuación de una diseminación hematógena postprimaria de bacilos.

7. Parece manifiesto que las típicas cicatrices apicales bilaterales no se hallan etiológicamente relacionadas con la infección tuberculosa.

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PRIMARY AND REINFECTION TUBERCULOSIS AS THE CAUSE OF DEATH IN ADULTS^{1,2}

An Analysis of 100 Consecutive Necropsies

E. M. MEDLAR³

In 1917, Opie (1) proposed an explanation for a differentiation between tuberculosis in the child and in the adult on the basis that adult tuberculosis is due to a reinfection. "First infection in almost all of those who reach adult life occurs in childhood and has the characters of a first infection in animals since it tends to implicate regional lymphatic nodes." "Apical tuberculosis usually exhibits the characters of a second infection, since it pursues a chronic course and is unaccompanied by tuberculosis of regional lymphatic nodes." Three facts are known, as of to-day, which would seem to warrant a review of the conclusions drawn by Opie. First, tuberculin surveys show that a considerable decrease in the incidence of tuberculous infection in young people has occurred in the past twenty-five years. Second, in recent years a considerable number of tuberculin-negative young adults have developed progressive tuberculosis which, from roentgenograms, cannot be distinguished from the "reinfection" type. Third, while tuberculosis in children has decreased appreciably, adult tuberculosis has not decreased in equal proportion.

The pathological changes observed in children and adults dying from tuberculosis at the present time show the same differences as were present twenty-five years ago. Large caseous lymph nodes continue to be a prominent feature in young children and an infrequent occurrence in adults. Calcified foci are frequently observed in adults and are rarely mentioned in children dying from this disease. On the basis that caseous lymph nodes are indicative of a progressive primary infection and calcified lymph nodes of a healed primary infection, it was thought that it might be possible to determine what proportion of adults were dying from a primary infection and what proportion from a reinfection. It appeared that no reliance could be placed on the presence or absence of calcified foci in the lung in distinguishing between primary and reinfection disease for two reasons: first, it is now known that small caseous foci in areas of endobronchial dissemination can calcify; second, since practically all cases exhibit cavitation to a greater or lesser extent, it would be impossible to determine with certainty whether a calcified primary focus had been present in the lungs.

MATERIAL AND METHOD OF PROCEDURE

One hundred consecutive necropsies on adults over 16 years of age who died from tuberculosis were thoroughly investigated with especial emphasis placed

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upon a painstaking study of the thoracic and abdominal lymph nodes. The material used came in very large part from the Chest Division of Bellevue Hospital.

The contents of the thorax were removed *en masse* and all lymph nodes found adjacent to bronchi, in the pleura and in the mediastinal contents were individually searched for macroscopic evidence of caseation, calcification and fibrosis. A similar procedure was used for the abdominal lymph nodes. The abnormal conditions and the location of the nodes in which lesions were observed were carefully recorded for each case. Fresh, unfixed specimens were examined on removal or soon thereafter. This procedure was chosen because formalin fixation hardens lymphoid tissue so much that fibrosis cannot easily be detected and discovery of minute foci of caseation and of calcification is rendered difficult. The lymph node texture was determined by palpation with bare fingers. Each node was sliced into sections about one millimeter in thickness with a sharp scalpel which proved of great value in the detection of minute foci of calcification and in appreciating the density of the tissue. It took from two to three hours to complete the examination of the lymph nodes in each case.

All lungs were carefully examined for the presence of cavity formation and, if more than one cavity was found, an estimate as to which cavity might be the oldest was made on the basis of fibrotic tissue and the appearance of the cavity wall. In those cases in which little pathological changes other than miliary tubercles were present, a careful search for the presence of small calcified foci which might represent the remnants of a healed primary infection was made. In such cases, the lung parenchyma was cut into slices of tissue about 5 millimeters in thickness and each slice was palpated with bare fingers. The mucosa of the entire gastro-intestinal tract was carefully inspected for the presence of tuberculous ulceration.

For a comparison of tuberculous infection in children with that in adults, 100 consecutive routine necropsy protocols of children below 10 years of age who died from tuberculosis in Bellevue Hospital were used. From each record was abstracted information as to involvement of lymph nodes in the thorax and in the abdomen, cavity formation in the lung and tuberculous ulceration of the intestine. In so far as the involved lymph nodes are concerned, these records did not contain as detailed information as was recorded in the adult cases used in this investigation, but in each protocol there was mention of the presence or absence of caseation in both thoracic and mesenteric nodes. It is possible that small caseous foci might have been observed in the nodes of those cases in which no lesions were mentioned had a very thorough search been made.

RESULTS

A comparison of the lesions found in the thoracic lymph nodes in the children and in the adults with reference to race is presented in table 1. There was a considerable variation in the number and size of the caseous nodes in the children, with the Negro children, as a whole, showing more extensive lymph node changes. Of the 6 children on whom there was no record of caseation or calcification in the

nodes, 5 were white children. In one of the 6 cases, no caseous focus was found in the lungs. This child had a tuberculous ulcer of the intestine with caseous mesenteric nodes and died from generalized miliary tuberculosis, apparently a primary intestinal infection. In the 5 remaining cases, small caseous parenchymal foci were described in 3 and subapical tuberculous cavities in 2 instances. Death was due to generalized tuberculosis with meningitis in 3, and extensive caseous pneumonia in 2 cases. The 3 cases with calcified nodes were white children all of whom had extrapulmonary tuberculous foci and died from generalized miliary disease, 2 having meningitis. In one case, a small puckered scar was observed in the lung, and in 2 cases, small caseous and calcified parenchymal foci were noted.

TABLE 1

*Condition of thoracic lymph nodes in individuals dying from tuberculosis
Children and adults compared according to race*

RACE	TOTAL	CONDITION OF THORACIC LYMPH NODES			
		Caseous	Calcified	Calcified and caseous	No caseation or calcification
Children under 10 years					
Total.....	100 (100%)	91 (91%)	*3 (3%)	—	†6 (6%)
White.....	63 (100%)	55 (87.3%)	3 (4.8%)	—	5 (7.9%)
Colored.....	37 (100%)	36 (97.3%)	—	—	1 (2.7%)
Adults over 16 years					
Total.....	100 (100%)	31 (34%)	26 (26%)	17 (17%)	‡23 (23%)
White.....	73 (100%)	18 (24.5%)	22 (30.1%)	13 (17.9%)	20 (27.6%)
Colored.....	27 (100%)	16 (59.3%)	4 (14.8%)	4 (14.8%)	3 (11.1%)

* 10 year white male, 4 year white male, 4 year white female.

† 10 year colored male, 8 year white male, pos. micro., 2½ year white male, 2 year white male, 1½ year white female, 1½ year white male.

‡ 13 examined microscopically, 12 had microscopic tuberculous foci.

In a number of the adult cases in which the lymph nodes are recorded as caseous, only a small focus, at times not over two millimeters in diameter, was found in a single node. Such lymph nodes were of normal size and appearance and the involvement would have been missed had not the nodes been cut into thin slices. In some cases, several lymph nodes were enlarged and entirely caseous. This condition was more frequently seen in the colored race.

The calcification noted varied from a single focus not over one or two millimeters in diameter in a single lymph node to one or two completely calcified nodes. In the cases where both calcified and caseous foci were observed, they were in all but 2 cases in lymph nodes which drained different areas of the pulmonary tissue. The areas of calcification were usually of small size and were

confined to one or two lymph nodes. The caseous foci were usually of small size but in a few instances the extent was as great as that found in cases in which caseous lymph nodes only were observed. Had not a thorough sectioning of all lymph nodes been done in every necropsy, the coexistence of calcified and caseous nodes would have been missed in nearly all of the cases. This is well illustrated by the case of a white male, 76 years of age, who died from generalized miliary tuberculosis with tuberculous meningitis. Two soft caseous nodes were easily demonstrated adjacent to a branch of the pulmonary artery to the right lower lobe with one of the nodes having eroded through the wall of the artery, thus becoming the source for the general dissemination. The pulmonary parenchyma directly supplied by this artery was so heavily seeded with tuberculous foci that no old parenchymal focus was found. On the left side, a two millimeter calcified focus in a single lymph node adjacent to the left lower lobe bronchus and a one millimeter calcified lesion in the parenchyma of the lower lobe 3 mm. beneath the diaphragmatic pleura were observed.

Failure to find either caseous or calcified foci in thoracic lymph nodes was wholly unexpected. In 2 of the 23 cases, calcified mesenteric nodes were present. In 21 cases, no macroscopic evidence of either caseation or calcification in lymph nodes was found anywhere. Macroscopic evidence of fibrosis was obtained in some of the cases but when this was present the distribution was bilateral and at times quite extensive. Because of the pattern and of the coexistence of a considerable degree of pneumoconiosis in such cases, the fibrosis was not regarded as evidence of a healed tuberculosis. Two-thirds of the cases revealed no macroscopic abnormality aside from the accumulation of black pigment. Histological sections were made of lymph nodes from 13 of the cases, some with and some without macroscopic evidence of fibrosis, and in 12 of them microscopic tuberculous foci were found irrespective of the presence or absence of fibrosis. This demonstrates that tubercle bacilli had gained entrance to the lymphatics and that a macroscopic examination of lymph nodes is inconclusive as to the presence or absence of minute tuberculous foci.

The differences in the lymph node changes between the child and the adult is evident. The extent of caseation of lymph nodes was, when present, considerably less in the adult, with individual exception. On the other hand, calcified foci and absence of macroscopic lesions were much more frequent in the adult. There is a somewhat similar difference between the white and the Negro adult.

The condition of the thoracic lymph nodes in relation to different age groups is presented in table 2. In the routine necropsies of children under one year of age, caseous lymph nodes were recorded in every case. The similarity in distribution of the different conditions in the lymph nodes in children above one year of age and in adults between 16 and 29 years of age is quite striking, especially with reference to the frequency of caseous foci and the infrequency of uninvolved lymph nodes. Contrariwise is the high incidence of calcified and of uninvolved lymph nodes and the very low incidence of caseous foci in cases over 50 years of age. This contrast in age groups suggests that perhaps the age of the individual more than a blockage of the lymphatics may have a bearing upon the type and the extent of tuberculous involvement of lymph nodes.

The possibility of a primary tuberculous infection originating in the intestinal tract is well known. It is necessary, therefore, to investigate the mesenteric lymph nodes in all tuberculous cases when the question of primary and reinfection disease is under consideration. And in such a study, the relationship of tuberculous cavity in the lung to tuberculous ulceration of the intestine and to caseous mesenteric lymph nodes must be determined. Such a comparison is presented in table 3.

In the children there was but a single case where it seemed probable that the primary infection occurred in the intestine, while in the adult 7 cases showed old calcified mesenteric nodes suggesting that at least this number may have had a primary intestinal infection. Caseous mesenteric nodes were recorded two and one-half times as often in the routine necropsy records of the children as the

TABLE 2

*Condition of thoracic lymph nodes in individuals dying from tuberculosis
Children and adults compared according to age*

AGE	TOTAL	CONDITION OF THORACIC LYMPH NODES			
		Caseous	Calcified	Calcified and Caseous	No caseation or calcification
Children under 10 years					
Total.....	100 (100%)	91 (91%)	3 (3%)	—	6 (6%)
Under 1 year .	26 (100%)	26 (100%) --	—	—	—
1 to 5 years...	54 (100%)	48 (88.8%)	2 (3.7%)	—	4 (7.5%)
5 to 10 years..	20 (100%)	17 (85%)	1 (5%)	—	2 (10%)
Adults over 16 years					
Total.....	100 (100%)	34 (34%)	26 (26%)	17 (17%)	23 (23%)
16-29.....	16 (100%)	12 (75%)	1 (6.3%)	1 (6.3%)	2 (12.4%)
30-49.....	49 (100%)	20 (40.8%)	8 (16.3%)	10 (20.4%)	11 (22.5%)
50 or older....	35 (100%)	2 (5.7%)	17 (48.6%)	6 (17.1%)	10 (28.6%)

author found them in the adult, while no calcified mesenteric nodes were mentioned in the records of the children.

The 38 cases with pulmonary cavities in the children were so recorded in the protocols. In addition, there were 4 cases in which bronchi, eroded by caseous lymph nodes, were considered as the source for caseous pneumonia. Several cases had a description of bronchogenic dissemination, and in these cases ulcerative tuberculous lesions discharging bacilli into the bronchi must have been present. Small cavities are often missed in pulmonary tuberculosis in children because of insufficient search. From these considerations, one may judge that tubercle bacilli had been swallowed by most, if not all, of the children in whom caseous mesenteric nodes were recorded and in whom tuberculous ulcers of the intestine were also found. Under the circumstances, it is significant to find such a close correlation between pulmonary cavitation, intestinal ulceration and caseous mesenteric nodes.

Only 21 of the 89 adult cases with tuberculous cavity in the lungs exhibited caseous mesenteric nodes, and no such nodes were found in 11 cases without pulmonary cavitation. Tuberculous ulcers of the intestine were present in one-half of the cases with pulmonary cavity and in none of the cases without it. Of the 21 cases which had caseous mesenteric nodes, 19 had tuberculous ulcers of the intestine. In 2 cases the author failed to find evidence of intestinal ulceration where caseous mesenteric lymph nodes were present.

TABLE 3

Relation of caseous mesenteric lymph nodes to cavity in the lung and ulceration of the intestine
Children and adults compared

MESENTERIC LYMPH NODES	TOTAL	LUNGS		INTESTINES	
		Cavity	No cavity	Ulcer	No ulcer
Children under 10 years					
Total.....	100	38 (100%)	62 (100%)	*40 (100%)	†60 (100%)
Caseous.....	43	25 (65.5%)	18 (29%)	35 (87.5%)	8 (13.3%)
No gross case- ation.....	†57	13 (34.5%)	44 (71%)	5 (12.5%)	52 (86.7%)
Adults over 16 years					
Total.....	100	89 (100%)	11 (100%)	45 (100%)	55 (100%)
Caseous.....	17	17 (19.5%)	—	15 (33.3%)	2 (3.6%)
Calcified.....	3	3 (3.4%)	—	1 (2.2%)	2 (3.6%)
Calcified and caseous	4	4 (4.5%)	—	4 (8.8%)	—
No gross cal- cification or caseation ..	76	65 (73%)	11 (100%)	25 (56%)	51 (92.8%)

* In 15 cases with intestinal ulcer, no pulmonary cavity was mentioned. In 6 of these cases, bronchogenic spreads, and in 4, ulceration of a bronchus were mentioned.

† 13 showed pulmonary cavity.

‡ 6 of these showed microscopic tubercles; 3 pulmonary cavity—3 no cavity; 4 with intestinal ulcer; 2 no ulcer.

Caseous thoracic lymph nodes were present in 18 of the 21 adult cases with caseous mesenteric lymph nodes; 10 had caseous nodes only in both situations; 5 had calcified and caseous thoracic and caseous mesenteric nodes; 2 had caseous thoracic with calcified and caseous mesenteric nodes; and in one case, calcified and caseous nodes were present in both sites. In the 3 remaining cases there were calcified thoracic nodes with caseous mesenteric nodes present in 2 and calcified and caseous nodes in one.

DISCUSSION

There are two facts with which all investigators will agree: first, a first infection with the tubercle bacillus in the child usually results in an extension from a

parenchymal focus through the lymphatics to regional lymph nodes which generally become entirely caseous; second, if and when the primary focus heals, calcified foci commonly remain as mute evidence of the healed infection. This relationship between parenchymal foci and lymph nodes in the drainage path, first reported by Parrot (2) in 1876 and later corroborated by Küss (3), Ghon (4), Opie (1), Schürmann (5), Sweany (6) and Terplan (7), to name a few, has had great influence upon the interpretation of tuberculous infection in the adult. Some investigators would not entirely agree with Schürmann (5) who maintains that this combination, commonly called the Ghon complex, is an absolute pathognomonic entity.

Disagreements appear in reports on primary infection in the adult. Ghon (4), Terplan (7) and Ragnatti (8) claim that the Ghon complex is the same in adults and children, although Ragnatti believes that a primary infection is rare after the age of 15 years. Sweany (9) found that primary infections in the adult behave differently from those in children. Opie (1) found that "almost all human beings are spontaneously 'vaccinated' with tuberculosis before they reach adult life." Blumenberg (10) observed that primary infections in adults are not characterized by involvement of lymph nodes, and he believes that this difference is influenced more by the age of the individual than by the allergic state.

A majority of investigators agree that phthisis is a reinfection phenomenon. Some think that this condition is the "relighting" of a smouldering unhealed focus derived from a primary infection which they call an "endogenous reinfection"—a wrong usage of the term reinfection.⁴ Others use the term reinfection in its correct meaning, that is, a new exogenous infection after a first infection has completely healed. Pinner (11), for instance, in discussing immunological principles relative to data obtained from animal experimentation states: "Only a well considered interpretation of the infection-reinfection experiments established the recognition that human phthisis is a reinfection tuberculosis, that infection and disease, identical in experimental animals, are two nosologically distinct entities in man, which in the animal can at best be approximated but can be reproduced only under exceptional circumstances." There seems to be general agreement that there is no lymph node involvement in a reinfection disease and an "allergic state" is claimed to be responsible for this phenomenon. Recently Terplan (12) has reported cases in which a reinfection found in persons dying from other causes behaved just like a primary infection; and the author has evidence, not yet published, which corroborates these observations. On this question, Rich (13) comments as follows: "For the present purpose, it is sufficient to recognize that, while occasional individuals may lose the resistance conferred by a primary infection to the extent that they will respond to reinfection with the development of a second primary type pulmonary lesion associated with enlargement of the regional lymph nodes, the result of studies all over the world have shown this event to be decidedly uncommon, regardless of the degree of exposure to infection."

⁴ In discussing terminology, Terplan (Supplement to *Am. Rev. Tuberc.*, August, 1940, page 5) advocates the term "endogenous reacclimation" for the process. (Editorial)

When the present study to determine the relative frequency of death from "primary" and "reinfection" tuberculosis in adults was begun, the dogma that caseous lymph nodes were indicative of a progressive primary infection and calcified lymph nodes of a healed primary infection was accepted. On this basis alone, 62 of the 100 cases could be clearly separated into two groups: (1) 34 adults died from a primary tuberculous infection with the youngest being 16 years of age and the oldest being 68 years of age; (2) 28 adults died from a reinfection tuberculosis with a range in age from 27 to 76 years. The pattern of the disease as a whole was indistinguishable in the two groups.

The finding of both caseous and calcified lymph nodes in 17 cases was not at all anticipated. Two explanations may be offered for this. First, one primary focus may have healed and a concomitant primary focus may have progressed. This explanation hardly seems plausible for the majority of the caseous lymph nodes resembled similar nodes observed in a primary infection and in a few cases the healed primary was in the intestine, thereby necessitating concomitant primary infection in lung and intestine with a difference of behavior in the two sites in each case. The second explanation, supported by Terplan's report (12) and the author's own observation, is that, following healing of a primary infection, a reinfection was incurred which acted like a primary infection. This, in so far as the author is aware, has been reported in but 2 cases dying from tuberculosis by Terplan (7). An incidence of 17 per cent in this series is certainly not in keeping with the observation of Rich (13). Perhaps an explanation of this unexpected discovery is the thoroughness with which the lymph nodes were investigated. The pattern of tuberculous infection resembled that observed in the two groups discussed above.

The group of 21 cases in which no macroscopic evidence of caseation or calcification in the lymph nodes was found brings up the question of incomplete primary complexes, that is, a pulmonary focus without lymph node involvement. Such a condition apparently has not entered the considerations on phthisis. Terplan (14) recently has reported as high as 28 per cent of incomplete primary complexes in cases dying from causes other than tuberculosis which corresponds fairly closely to an incidence of 21 per cent in the group dying from tuberculosis observed in this study. In these cases one is in a quandary as to how to classify them. Are they cases of reinfection in which an incomplete primary complex has healed, or are they examples of progressive incomplete primary complexes? The literature on tuberculosis contains an occasional mention of incomplete primary complexes, but because of its apparent infrequency little serious consideration has been given the phenomenon. When, however, the position is taken that phthisis is a reinfection tuberculosis, as is done by Pinner,⁵ Opie and

⁵ Pinner, in his discussion of "Incipient Pulmonary Tuberculosis as a Direct Consequence of Late Primary Infection," ends his discussion as follows: "This whole problem of primary pulmonary tuberculosis in adults has, so far, found but little attention in U.S.A. It is entirely possible that these primary forms of pulmonary tuberculosis in adults are less frequent and less severe in this country than in some parts of Europe." (Pulmonary Tuberculosis in the Adult, 1945, page 272.) It is the belief of the author that fatal primary pulmonary tuberculosis acquired in adult life is more frequent than is generally appreciated in this country.

others, the question of incomplete primary complexes becomes very important. In this series, it involved one-fifth of the cases. Here again, the pattern of disease differed not at all from that observed in the other groups.

From the foregoing discussion, it is apparent that tuberculosis in the adult can hardly be placed in one all-inclusive group, that is, reinfection disease; or explained by a single phenomenon, that is, hypersensitivity at high tide or low ebb. Hypersensitivity may well be a *product* of rather than a *cause* of the pathological processes observed. To the author, the lack of uniformity in the cases seems to fit in very well with the way Nature works. Concepts of a disease process are enhanced by a proper integration of the variables observed, whether they be observed in natural or experimentally produced disease. Not infrequently this integration results in a realignment of accepted concepts. Such would seem to be the case in tuberculous disease in the adult for it appears that the peculiar pattern of phthisis can result from either a reinfection or a progressive primary disease.

From the data obtained from this investigation it is possible to assemble groups of cases which would either confirm or refute the divergent views now held by different authors. For instance, Blumenberg's idea that age rather than allergy influences lymph node involvement can easily be supported but a different assembly of cases would indicate that allergy might have the greater influence. It is frequently argued that the reason caseation of lymph nodes does not occur in reinfection disease is that the allergic state aids in localizing the bacilli so that they cannot gain access to the lymphatics. Contrariwise, it can be shown that, in most cases of reinfection, microscopic tuberculous foci are present in lymph nodes in the path of drainage and it can be argued that the lack of development of extensive caseation is due to unfavorable growth conditions in the lymphoid tissue.

Roentgenological studies of adults with so-called reinfection tuberculosis fail to reveal any calcified foci in the thorax in the majority of the cases. Enlarged lymph nodes, indicative of extensive caseation, are infrequently observed in adults who develop a "reinfection type" of disease after a conversion from a negative to a positive tuberculin sensitivity. The reasons for this condition are readily given. The calcified remnants of a healed primary infection are frequently too small to be recognizable roentgenologically, or are so placed that they would not be evident in the usual roentgenographic positions. The amount of caseation in lymph nodes in primary tuberculosis in the adult is very frequently too little to cause any appreciable enlargement of the nodes. It is no wonder that the most ardent supporters of the dogma that phthisis is a "reinfection" tuberculosis are unable to differentiate roentgenologically between a primary and a reinfection disease in the adult.

Opie (1) and Terplan (7) are advocates of roentgenograms of excised lungs in studies such as the one under discussion. The author agrees that small calcified foci, especially in the lung, may be more quickly and easily detected by roentgenograms but small foci of caseation and of fibrosis will fail to be registered in the films. It would be most unfortunate to have the roentgenogram replace experienced sight and trained palpation in the examination of fresh tissues. If the

roentgenograms of excised lungs are utilized there still remains the necessity for very thorough dissection to reveal small foci not visualized in the roentgenograms.

A fairly definite idea of the location of the oldest cavity was possible in the majority of the cases and, with one exception, the location was in the upper portions of pulmonary lobes. In the exception, the small cavity was in the diaphragmatic portion of a lower lobe. The cases showed the usual and peculiar pattern of phthisis. This occurred in both primary and reinfection cases, provided it was possible to establish on morphological grounds a distinction between primary and reinfection disease. It would seem that entirely too much emphasis has been placed upon *reinfection* as THE cause of phthisis.

That a large majority of individuals localize and heal primary tuberculous infections is evident from the frequent calcified primary complexes found at necropsy. It is probable that many reinfections are also similarly handled although proof of this is not so readily obtained. Apparently the factors which permit the development of a progressive disease are peculiarities of certain areas of lung tissue and of conditions within an individual which to date have escaped detection. One evident fact is that an ability to heal a first infection is no guarantee that a subsequent infection will be similarly controlled. Whenever tuberculous foci in upper portions of pulmonary lobes progress to the state that they assume clinical significance, which includes the early indistinct roentgenographic shadows of "minimal" disease, the condition is of serious import irrespective of whether it is a primary or a reinfection lesion, and also irrespective of the age of the adult. It would seem advisable to relegate the present concept of phthisis as a "reinfection" disease to a place of lesser importance for by no means can it explain all cases of progressive disease in adults.

CONCLUSIONS

1. An analysis of 100 adults dying from tuberculosis is presented with reference to the incidence of "primary" and "reinfection" disease on the dogma that caseous nodes indicate a progressive primary infection and calcification in lymph nodes a healed primary infection. In this connection, the term reinfection is used in the sense that a previous infection had been healed.

2. Thirty-four per cent of the cases died from a primary infection. Twenty-eight per cent of the cases died from a reinfection. Seventeen per cent had both calcified and caseous nodes and may be interpreted as dying from a reinfection disease which acted like a primary infection. Twenty-one per cent of the cases had neither caseous nor calcified nodes. They may be regarded as dying from (1) a progressive incomplete primary complex tuberculosis or (2) a reinfection disease in which an incomplete primary complex had healed.

3. The pattern peculiar to phthisis was present in these cases irrespective of the conditions observed in the lymph nodes.

4. It is evident that all cases of progressive pulmonary tuberculosis in the adult cannot be explained on the basis of a reinfection, and it would appear to be equally difficult to explain them on the generally accepted interpretation of the influence of hypersensitivity in reinfection.

5. For the development of progressive pulmonary tuberculosis, that is, phthisis in the adult, it is essential that the tubercle bacillus become lodged in the cephalic portions of pulmonary lobes whether it be a first or a subsequent infection. Beyond this fact all explanations are nebulous and await clarification.

CONCLUSIONES

La Incidencia de la Tuberculosis Primaria y de Reinfección como Causa de Muerte en el Adulto

1. Este análisis de 100 personas adultas que murieron de tuberculosis preséntase con referencia a la incidencia de enfermedad "primaria" y de "reinfección", a base de la teoría de que los ganglios caseosos indican infección primaria evolutiva y los calcificados infección primaria cicatrizada, usándose el término de reinfección en el sentido de que una infección previa ha cicatrizado.

2. Un 34 por ciento de los enfermos murieron de una infección primaria, y un 28 por ciento de una reinfección. Un 17 por ciento tenían tanto ganglios calcificados como caseosos, pudiendo interpretarse la muerte como debida a una reinfección que actuó como infección primaria. En 21 por ciento de los casos no había ganglios caseosos ni calcificados, y la muerte puede considerarse como debida a: (1) una tuberculosis compleja primaria incompleta evolutiva o (2) una enfermedad tipo reinfección después de haber curado un complejo primario incompleto.

3. Independiente del estado observado en los ganglios linfáticos, en estos casos existía el patrón peculiar de la tisis.

4. Es manifiesto que no pueden explicarse a base de reinfección todos los casos de tuberculosis pulmonar evolutiva en el adulto, y parece igualmente difícil explicarlos tomando la interpretación aceptada generalmente del influjo de la hipersensibilidad en la reinfección.

5. Para el desarrollo de la tuberculosis pulmonar evolutiva, es decir, tisis, en el adulto es indispensable que el bacilo tuberculoso se aloje en las porciones cefálicas de los lóbulos pulmonares ya se trate de infección primaria o subsiguiente. A partir de ahí todas las explicaciones resultan nebulosas y necesitan esclarecimiento.

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STREPTOMYCIN SENSITIVITY OF TUBERCLE BACILLI¹

Studies on Recently Isolated Tubercle Bacilli and the Development of Resistance to Streptomycin *in vivo*

GUY P. YOUNG² AND ALFRED G. KARLSON³

Using the H37 strain of *Mycobacterium tuberculosis*, Schatz and Waksman (1) first demonstrated that tubercle bacilli were susceptible *in vitro* to the bacteriostatic action of streptomycin. Subsequently, Youmans (2) discovered that the growth of 5 additional strains of virulent, human type tubercle bacilli was decidedly inhibited *in vitro* by streptomycin. Feldman, Hinshaw and Mann (3) have proved that streptomycin has a marked suppressive action on experimental tuberculosis of guinea pigs, and Youmans and McCarter (4) have found this agent effective in the control of experimental tuberculosis of white mice.

It has been noted that with other bacteria (5) there is considerable variation in sensitivity to streptomycin between different strains of the same species. For this reason it was advisable to determine not only the sensitivity of strains of tubercle bacilli isolated from patients before treatment with streptomycin was started but also the range of sensitivity to streptomycin likely to be encountered among recently isolated strains of tubercle bacilli. The relative sensitivity of human, bovine and avian strains of tubercle bacilli to streptomycin was also determined.

In a preliminary communication by Youmans, Williston, Feldman and Hinshaw (6) it was reported that tubercle bacilli became resistant when exposed to streptomycin either *in vivo* or *in vitro*. The present paper reports further observations on the development of resistance to streptomycin by tubercle bacilli, isolated from patients who were undergoing treatment with this agent.

Observations on the development of resistance to streptomycin *in vitro* will be reported in a separate communication.

METHODS

Isolation of the strains of tubercle bacilli were made chiefly from a large number of patients who were suffering from various clinical types of tuberculosis; a few specimens were obtained at necropsy. Specimens of sputum and gastric washings from each patient were mixed with an equal volume of 3 per cent solution of sodium hydroxide, shaken in a Kahn shaker for fifteen minutes and placed in an incubator at 37°C. for thirty minutes. The mixture was then neutralized with 8.7 per cent solution of hydrochloric acid and centrifuged. The sediment was transferred to four tubes of glycerinated egg-yolk agar and four tubes of egg-yolk agar which contained no glycerine.⁴ Urine and suspensions

¹ This work was aided in part (G. P. Y.) by a grant from Parke, Davis & Company, Detroit, Michigan.

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⁴ Nonglycerinated medium, as well as that which contains glycerine, is used in the culture of all specimens from new patients to facilitate the isolation of any bovine strains, since bovine strains do not grow well, on original isolation, in the presence of glycerine.

of tissues were treated with oxalic acid according to the method of Corper and Uyei (7) and cultures were made in the manner just described.

Cultures were examined weekly. Selections for tests of sensitivity to streptomycin were made when colonies were large enough to be scraped off and placed in suspension, usually after three to six weeks of incubation.

The sensitivity of the strains to the bacteriostatic action of streptomycin was determined by a modification of the method previously described (2-7). This method, in detail, is as follows:

A modified Proskauer and Beek synthetic medium of the following composition was employed:

Asparagin	0.5 per cent
Monopotassium phosphate	0.5 per cent
Potassium sulfate	0.05 per cent
Glycerol	2.0 per cent

The above ingredients are dissolved in the order given in distilled water, care being taken that each ingredient is completely dissolved before the next is added. The hydrogen ion concentration is then adjusted to pH 7.0 with 40 per cent sodium hydroxide, then add:

Magnesium citrate 0.15 per cent

This constitutes the basic medium which is sterilized in the autoclave at 15 lbs. pressure for twenty minutes. To this medium is then added aseptically, for the purpose of obtaining more rapid growth, enough sterile human, bovine or horse plasma or serum to make a final concentration in the medium of 10.0 per cent. The plasma or serum is sterilized by filtration through a Berkefeld or other suitable bacteriological filter.

Glassware: All glassware, tubes, flasks, pipettes, etc., should be thoroughly cleaned with either soap and water or cleaning solution and rinsed seven to eight times with tap water and three to four times with distilled water.

Test tubes of any size may be employed, but care must be taken to adjust the volume of medium per tube to the size of the test tube. The maximum volume of medium used in test tubes 200 x 25 mm. is 10.0 ml. In test tubes 150 x 20 mm. the volume should not exceed 5.0 ml. Smaller volumes can be used to advantage. One of us (A.G.K.) employed 4.0 ml. volumes in 15 x 150 mm. test tubes. All glassware, including pipettes, is sterilized in the autoclave at a pressure of 20 lbs. for twenty minutes.

Streptomycin dilutions: Streptomycin⁵ is dissolved aseptically in the above medium in whatever concentration may be desired. We routinely employ twofold dilutions which range from 100 micrograms per ml. to 0.095 micrograms per ml. Higher concentrations are employed as needed. When preparing serial dilutions it is important to use separate pipettes for each dilution. Otherwise, not only will the dilutions be inaccurate but, due to carry over, inhibition of growth may occur several tubes lower than it should.

Since we have found that the potency of streptomycin was not lost even when the medium in which it was contained was stored in the refrigerator at 10°C. for as long as five weeks, it is economical to prepare as many as a hundred tubes of each concentration of streptomycin at one time and store them for future use.

⁵ Furnished to A. G. K. through the courtesy of Merck & Co., Rahway, New Jersey. Furnished to G. P. Y. through the courtesy of Dr. L. A. Sweet, Parke, Davis & Company, Detroit, Michigan.

Preparation of suspensions of tubercle bacilli: A few flakes of growth of the tubercle bacillus strain to be tested are placed in one drop of 0.01 molar phosphate buffer or medium in the bottom of a sterile mortar. These are ground by hand for a few minutes until a relatively homogeneous suspension is obtained. This is diluted to a volume of 5 to 15 ml. by the gradual addition of sterile buffer solution. The resulting suspension is then transferred to a sterile test tube and allowed to stand for thirty minutes. The larger coarse clumps will settle out leaving a relatively fine homogeneous supernatant suspension. This supernatant suspension is transferred by decantation or aspiration to a sterile test tube. Ten to 15 such suspensions can easily be prepared in an hour.

These suspensions may be standardized in several ways. Since a tenfold variation in the amount of inoculum will not affect the endpoints of streptomycin sensitivity, an accurate standardization is not necessary. However, an inoculum should be chosen that will give good growth in a relatively short time and yet not be so large that false growth readings will be made.

The best, and most rapid, method of standardization is the use of turbidimetric measurements in any suitable photoelectric colorimeter.

If such an instrument is not available, use of Hopkins vaccine centrifuge tubes is rapid and not laborious. An aliquot of 1 to 5 ml. of each suspension is transferred to a Hopkins vaccine centrifuge tube and centrifuged at high speed for thirty minutes. The packed tubercle bacilli in the tip of the tube are measured in terms of cubic millimeters and arbitrarily each cubic millimeter is assigned a wet weight of 1.0 milligram.

After standardization the suspensions are diluted so as to contain the desired inoculum for each tube in 0.1 or 0.2 ml. of phosphate buffer or medium. The inoculum to be preferred should be from 0.1 to 0.5 mg. for each tube (wet weight Hopkins tube value).

Duplicate tubes of each streptomycin dilution and appropriate control tubes of medium are inoculated with 0.1 or 0.2 ml. containing the desired amount of tubercle bacilli. The tubes should be inoculated rapidly to minimize the settling out of tubercle bacilli in the pipette. The tubes should be shaken vigorously after being inoculated and then incubated at 37°C.

Growth of tubercle bacilli will frequently be evident as early as two to three days and final readings can often be made as early as four to five days after inoculation. However, since larger amounts of growth are easier to observe, we have found that an incubation period of seven to fourteen days is the most satisfactory before making the final reading.

In this medium the tubercle bacilli grow at the bottom and up the sides of the tube leaving the supernatant clear. When the tubes are gently shaken flakes of tubercle bacilli swirl through the medium. This flaky type of growth is very characteristic and with a little experience is readily distinguished from any contaminating organism.

The least amount of streptomycin which completely prevents this subsurface (submerged, deep-seated) growth is recorded as the streptomycin sensitivity of the strain being tested.

The reliability of the method described for determining the sensitivity of tubercle bacilli to streptomycin is such that no significant differences were obtained when the same strains were tested independently in separate laboratories. Duplicate tests and repeated examinations of the same cultures for several months gave similar results. The variation was never greater than a plus or minus one dilution; the inherent error of the method.

RESULTS

In table 1 are tabulated the results on the tests of 131 recently isolated strains of tubercle bacilli for sensitivity to streptomycin. These strains were, essentially,

tubercle bacilli of human type; animal typing tests for pathogenicity were not done. The results show that a majority of the strains were highly sensitive to the bacteriostatic action of streptomycin: 90 per cent of them were inhibited by a concentration of less than 2 micrograms of streptomycin per cc. of medium. None of the strains exhibited an extremely high natural resistance to streptomycin. All of these strains were obtained from patients prior to treatment with streptomycin.

TABLE 1

Sensitivity of 131 recently isolated human strains of tubercle bacilli to streptomycin

STRAINS (131)	EFFECTIVE CONCENTRATION OF STREPTOMYCIN, MICROGRAMS PER ML.
6	0.095
26	0.19
44	0.39
26	0.78
16	1.56
9	3.12
3	6.25
1	12.5

TABLE 2

Sensitivity of 16 bovine and 14 avian strains of tubercle bacilli to streptomycin

BOVINE STRAINS (16)	EFFECTIVE CONCENTRATION OF STREPTOMYCIN, MICROGRAMS PER ML.
3	0.095
5	0.19
4	0.39
2	0.78
1	1.56
1	3.12
AVIAN STRAINS (14)	
1	0.39
2	1.56
5	3.12
2	6.25
3	25.0
1	50.0

In table 2 are reported the results of tests of 16 known bovine and 14 known avian strains of tubercle bacilli for sensitivity to streptomycin. The degree of sensitivity of bovine strains appears to be of about the same order as that of human strains. A majority of the avian strains appear to have greater natural resistance to the bacteriostatic action of streptomycin than do human or bovine strains.

TABLE 3

Sensitivity to streptomycin of tubercle bacilli isolated from patients during treatment with streptomycin

CASE NUMBER	SOURCE OF ORGANISMS	STREPTOMYCIN			
		Days administered	Average daily dose, mg.	Total administered, g.	Effective concentration, micrograms per ml.
1	Urine	29	0.1 to 0.2	3.6	3.12
1	Urine	71	0.5 to 1.0	61.1	1,000.0
2	Guinea pig* spleen	92	2 to 4	238.0	>1,000.0
3	Draining craniotomy wound	38	0.5	19.0	3.12
4	Gastric contents	56	1.5	84.0	>1,000.0
5	Urine	0	0	0	0.035
5	Kidney†	38	0.5 to 1.0	30.7	100.0
6	Gastric contents	0	0	0	0.39
6	Gastric contents	131	1 to 2	192.0	>2,500.00
7	Spinal fluid	0	0	0	0.78
7	Meninges‡	48	1 to 2	58.1	500.0
8	Gastric contents	0	0	0	0.78
8	Gastric contents	78	1.0	78.0	>2,000.0
9	Gastric contents	0	0	0	0.78
9	Gastric contents	131	1 to 3	261.0	>2,000.0
10	Axillary abscess	36	1.0	31‡	0.095
11	Sputum	30	1.7	51.0	0.39
12	Spinal fluid	88	2.5	220.0	10.0
13	Lung‡	42	0.5 to 10.0	242.5	1.56
14	Gastric contents	30	3.0	90.0	0.39
14	Gastric contents	60	3.0	180.0	>2,000.0
15	Urine	34	1.8	61.2	0.78
15	Urine	46	1.8	82.8	>2,500.0

* Inoculated with urine from patient.

† Surgical specimen.

‡ Specimen obtained at necropsy.

§ Patient received less than 1 g. on a few days.

In table 3 are presented the results of tests for sensitivity to streptomycin made on cultures of tubercle bacilli isolated from patients during the course of

treatment with streptomycin. In addition, in cases 5, 6, 7, 8 and 9 the results of tests for sensitivity to streptomycin made on strains isolated prior to treatment are also given; these results, along with others, were also used in preparation of the data presented in table 1.

The data presented in table 3 are not complete enough to warrant conclusions as to clinical significance but certain facts are apparent. Cultures isolated from patients who have been given 1 to 2 g. of streptomycin daily for several months may have much greater resistance to the drug *in vitro* than cultures isolated prior to treatment. Whether this increase in resistance to the drug is gradually acquired by the tubercle bacilli or appears suddenly as a result of survival of resistant strains normally present is not discernible from our data. Of special interest in this regard is case 15 in which tubercle bacilli in cultures of urine obtained thirty-four days after treatment was started were sensitive to streptomycin in concentration of 0.39 micrograms per cc., whereas tubercle bacilli in cultures obtained twelve days later were resistant to the substance in concentration of more than 2,500 micrograms per cc.

The method used for determining the sensitivity of tubercle bacilli to streptomycin permits detection of only those bacilli which have the greatest resistance to the drug; such bacilli are detected even though they may be present in a culture in exceedingly small numbers. We have not determined whether or not both sensitive and resistant strains may be present in the same cultures.⁶ At present we do not know what clinical significance may be attached to the presence of streptomycin-resistant strains of tubercle bacilli in treated patients.

CONCLUSIONS

The majority of tubercle bacilli isolated from patients prior to treatment with streptomycin are sensitive *in vitro* to streptomycin in concentrations of less than 2 micrograms per ml. of medium. Ninety per cent of 131 strains studied were inhibited by the drug in concentration of 1.56 micrograms or less per ml. of a liquid medium which contained 10 per cent horse, beef or human plasma.

Bovine strains of tubercle bacilli apparently exhibit the same order of sensitivity to streptomycin as those of the human type.

Avian strains of tubercle bacilli are somewhat more resistant to the action of streptomycin *in vitro* than are mammalian strains.

Cultures of tubercle bacilli isolated from patients after several months or more of treatment with streptomycin exhibit resistance to streptomycin *in vitro* several thousand times as great as that of cultures isolated prior to treatment.

The clinical significance of the resistance to streptomycin developed by tubercle bacilli is not definitely established.

CONCLUSIONES

Sensibilidad de los Bacilos Tuberculosos a la Estreptomicina

La mayoría de los bacilos tuberculosos aislados de los enfermos antes de recibir la estreptomycinoterapia son sensibles *in vitro* a la estreptomicina a concentra-

⁶ This phase of the question is now under investigation in the laboratory of one of us (A. G. K.).

ciones de menos de 2 microgramos por ml. de medio. Noventa por ciento de 131 cepas estudiadas fueron inhibidas por la droga a una concentración de 1.56 microgramos o menos por ml. de un medio líquido que contenía 10 por ciento de plasma equino, bovino a humano.

Las cepas bovinas de los bacilos tuberculosos manifiestan aparentemente el mismo tenor de sensibilidad a la estreptomicina que las del tipo humano.

Las cepas aviarias son algo más resistentes a la acción de la estreptomicina *in vitro* que las de mamífero.

Los cultivos de bacilos tuberculosos aislados de enfermos tratados por varios meses con estreptomicina manifiestan una resistencia *in vitro* a la estreptomicina varios miles de veces mayor que los cultivos aislados antes del tratamiento.

No se ha establecido definitivamente el significado clínico de la resistencia a la estreptomicina desarrollada por los bacilos tuberculosos.

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STREPTOMYCIN RESISTANT STRAINS OF TUBERCLE BACILLI^{1,2,3}

Production of Streptomycin Resistance *in vitro*

ELIZABETH H. WILLISTON AND GUY P. YOUNG

That the sensitivity of bacteria to certain antibiotics can be altered by continued exposure both *in vivo* and *in vitro* has been shown by many investigators. The publications of Selbie, Simon and McIntosh (1) and of Gallardo (2) and others report the appearance of penicillin-resistant strains of *Staphylococcus aureus* in patients treated with penicillin. Resistance to penicillin has also been produced *in vitro*. In this connection Abraham, Chain and collaborators (3), McKee and Houek (4), Rantz, Lowell and Kirby (5), Rammelkamp and Maxon (6), and others have succeeded in producing penicillin-resistant strains of a number of pathogenic bacteria by repeated exposure in broth cultures to increasingly higher concentrations of the drug.

Buggs, Bronstein and associates (7) reported in 1946 that streptomycin-resistant strains had been isolated from patients receiving treatment with that drug. *Staphylococcus albus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, alpha hemolytic streptococci, diphtheroids and possibly *Aerobacter aerogenes* and beta hemolytic streptococci were shown to develop such resistance in the patient. Streptomycin resistance was induced *in vitro* in 4 strains of gonococcus and 9 strains of meningococcus by Miller and Bohnhoff (8).

In a preliminary report Young, Williston, Feldman and Hinshaw (9) showed that some strains of tubercle bacilli isolated from patients under streptomycin treatment showed a marked resistance, indicating that this organism is not an exception in its response to repeated exposure to the drug in the patient. At this time, 2 strains of *Mycobacterium tuberculosis* had been exposed to streptomycin *in vitro* and had developed an increase in resistance of over a thousand-fold. The present paper details the results obtained following exposure of 18 strains of *M. tuberculosis* to streptomycin *in vitro*.

METHODS

The cultures used were avian, bovine and human strains⁴ including the standard H37-Rv. The human and bovine strains had been isolated recently from patients with active tuberculosis who, with 2 exceptions (cases 6 and 97), had had no streptomycin therapy previous to culturing.

Synthetic medium containing plasma and streptomycin was prepared as described by

¹ From the Department of Bacteriology, Northwestern University Medical School, Chicago, Illinois.

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³ Streptomycin was furnished through the courtesy of Dr. L. A. Sweet, Parke, Davis & Company, Detroit, Michigan.

⁴ Strains used are included in the article reported by G. P. Young and A. G. Karlson on page 529 in this journal.

Youmans (10, 11). This was tubed in 5 ml. amounts in test tubes 20 by 150 mm. Suspensions of the tubercle bacilli selected for exposure were made in .01 molar potassium phosphate buffer at pH 7.0 and 0.25 mg. of these suspensions served as the inoculum for each tube. The streptomycin dilutions ranged from 1,000 micrograms to 0.095 micrograms per ml. and consisted of 13 different dilutions. Exposing the culture each time in all dilutions served both to make the exposure and to measure the amount of resistance developed. At one- to two-week intervals transfer was made from the tube showing growth and containing the greatest amount of streptomycin.

Two methods were used for this reëxposure of a given strain to streptomycin. In one, the bacteria from the streptomycin tubes were planted on egg medium and incubated till the growth was abundant enough to grind and resuspend for a further exposure. In the second method the organisms from the tube with the most streptomycin showing growth were used as inoculum for all the tubes of the next exposure. Neither method showed any consistent advantage over the other.

At intervals comparative tests using the parent strain of the test organism were run. A test of the potency of the streptomycin dilutions was made by planting the H37Rv strain in a series of dilutions from each batch of medium used. Within the limit of error of the method this strain was inhibited by the same amount of streptomycin each time.

RESULTS

Nine strains of *M. tuberculosis* (7 human, one avian and one bovine) developed at least a thousandfold resistance to streptomycin (table 1). The time of exposure varied from 52 to 120 days. Nine other strains (one bovine) showed somewhat less increase of resistance when exposed from 66 to 117 days. Of these last, 3 developed only a fourfold resistance and one developed only a twofold resistance after eighty-five days.

Table 1 shows the total time in days each culture was incubated in the presence of streptomycin. In view of the fact that the streptomycin slowly decreases in potency during incubation, these figures do not indicate the true concentration of streptomycin.

The rate at which the resistance to streptomycin increased followed no particular pattern, at least so far as the method used could detect. Some cultures showed a rather steady increase in the amount of streptomycin they could withstand in successive culture generations; others made little progress in three or four culture generations and then suddenly increased markedly in resistance.

As has been noted previously by Youmans (10), nonresistant strains of *M. tuberculosis* in the synthetic medium plus plasma gave a rather sharp line of demarcation between the dilutions which inhibited and those which did not inhibit. Some strains which had been exposed to streptomycin for several generations showed a tendency to "taper off," to give slight growth in 4 or 5 dilutions more potent than the one which permitted abundant growth.

After a strain had become resistant to 1,000 micrograms it was planted on Herrold's egg agar slant and tested from time to time to detect any loss of this property. One strain, H37Rv, was observed for eleven months and failed to show any loss of resistance. The other strains showed no marked change of resistance after four to six months.

One ml. amounts of a filtrate of a culture of resistant H37Rv were added to a dilution series of streptomycin in broth and plasma and inoculated with a sensitive strain of H37Rv. The streptomycin showed no lack of potency in the presence of the filtrate.

TABLE 1
Streptomycin resistance developed in vitro of strains of M. tuberculosis

STRAIN AND TYPE	SOURCE	LEAST AMOUNT OF STREPTOMYCIN IN MICROGRAMS PER ML. REQUIRED TO INHIBIT COMPLETELY GROWTH OF ORIGINAL CULTURE	STREPTOMYCIN RESPONSE AFTER EXPOSURE (MICROGRAMS PER ML.)	TOTAL NUMBER OF DAYS EXPOSED
<i>Human</i>				
1	Sputum	0.195	>1000	94
23	Gastric washing	0.78	>1000	96
24	Gastric washing	0.19	>1000	86
52	Gastric washing	3.125	>1000	57
60	Lymph node	0.095	>1000	91
100	Gastric washing	1.56	>1000	120
<i>Bovine</i>				
69	Urine	0.095	>1000	99
<i>Avian</i>				
40	Stock culture	3.12	>3200	52
<i>Human</i>				
H37Rv		0.78	>1000	63
H37Rv		0.78	>1000	56
6	Urine	3.12	12.5	98
15	Gastric washing	0.78	3.125	66
20	Gastric washing	0.78	50.0	100
21	Gastric washing	0.39	3.125	77
97		1.56	500.0	112
110	Cervical lymph nodes	0.78	500.0	108
117		1.56	12.5	92
120	Sputum	1.56	3.125	85
<i>Bovine</i>				
118	Urine	0.39	1.56	117

Patients from whom 7 of the strains were isolated subsequently received streptomycin and eventually developed streptomycin resistant strains *in vivo* (strains 24, 100, 69, 6, 15, 20, 118 (table 1)).

SUMMARY

Fourteen out of 18 strains of *M. tuberculosis* developed definite resistance to streptomycin when cultured for successive generations in synthetic broth with plasma and streptomycin. Three strains showed only a fourfold increase in resistance, and one only twofold. There was a wide variation in the rate at

which the resistance developed. Nine strains showed at least a thousandfold increase in resistance after from 52 to 120 days' exposure; other strains showed less increase of resistance. Resistance was maintained for as long as eleven months.

SUMARIO

Cepas Estreptomicino-resistentes de los Bacilos Tuberculosos

Catorce de 18 cepas del *M. tuberculosis* mostraron resistencia bien definida a la estreptomicina después de ser cultivados durante generaciones sucesivas en caldo sintético con plasma y estreptomicina. Tres cepas sólo cuadruplicaron su resistencia, y una sólo la dobló. Varió sumamente la rapidez con que se desarrolló la resistencia. Nueve cepas revelaron un aumento por lo menos de mil en su resistencia al cabo de una exposición de 52 a 120 días; otras revelaron menos aumento. La resistencia se mantuvo hasta once meses.

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THE EFFECT OF GLYCEROL AND RELATED SUBSTANCES ON THE GROWTH AND THE OXYGEN UPTAKE OF THE TUBERCLE BACILLUS^{1, 2}

HUBERT BLOCH, E. MATTER AND EMANUEL SUTER

Glycerol is known to play a particular part among the nutrients in the culture of *M. tuberculosis* in synthetic media. For most strains, glycerol is the best or even the only usable source of carbon. On the other hand, if tested in the Warburg apparatus as substrate for bacterial cell metabolism, there are many respiration-promoting compounds with much more intensive effects than glycerol, belonging to various chemical groups, for example, aliphatic acids and alcohols, derivatives of benzoic acid, carbohydrates, etc. There does not seem to exist any direct relation between the growth- and the respiration-promoting faculty of a substance. On the contrary, a respiration-promoting substance can promote as well as inhibit bacterial growth, or even be without any influence on it (Bloch, 1942). Considering these facts it is not surprising that the respiratory effect of glycerol does not correspond to its outstanding growth-promoting ability. However, it was promising to compare the action of glycerol with that of chemically related compounds, with the aim of gaining a better understanding of the structural properties of substances, necessary, if they are to act both as respiratory stimuli and as growth-promoting compounds.

MATERIALS

We used the following substances for our experiments:

- (I) *Natural glycerol.*
- (II) *Synthetic glycerol:* Prepared from isopropylalcohol according to Bloch, Erlenmeyer and Furger (1944).
- (III) *α -monoacetylgllycerol:* From acetyl-acetone-glycerol according to Fischer and Pfähler (1920).
- (IV) *α - α' -diacetylgllycerol:* From glycerol and glacial acetic acid (Seelig, 1891; Geitel, 1897; Wegschneider, 1913).
- (V) *Triacetylgllycerol:* From glycerol and acetic anhydride (DRP 347 897; Friedländer, 14, 159, 1921).
- (VI) *Acetone glycerol:* Prepared according to Fischer (1895).
- (VII) *C-methyl glycerol:* From crotyl alcohol and HOCl by saponification with NaOH (Batalin and coworkers, 1937; Delaby, 1922). The compound is prepared, therefore, like II, not from glycerol, but by purely synthetic methods.
- (VIII) *Glycerol- α -monomethylether:* From Na methylate and glycerol monochlorhydrine (Grün and Bockisch, 1908).
- (IX) *Glycerol- α -monoisoamylether:* Prepared by pouring α -monochlorhydrine through a dropping funnel into a boiling 2 per cent solution of isoamyl Na-alcoholate in isoamyl alcohol. BP₁₄: 130–132°C.

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² Studies on the metabolism of tubercle bacilli, No. IX.

- (X) α - α -diglyceroether: $\text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CH}_2\text{—O—CH}_2 \cdot \text{CHOH} \cdot \text{CH}_2\text{OH}$ Preparation: 400 g. polyglycerol (prepared by heating glycerol with 1 per cent NaOH to 250°C.); 1,500 g. acetone; 10 cc. concentrated HCl, six hours at 30°C., while stirring. The polyglycerol dissolves only partially. Neutralize with dry Na_2CO_3 , filter and distill. Dissolve the fraction 120–200°C. (14 mm.) in water and extract the diacetone-diglycerol ether with ether. BP₁₄: 138–140°C., yield 31 g. Dilute with 30 cc. water and keep for two hours at 50–60°C. after adding one drop concentrated H_2SO_4 . Neutralize with BaCO_3 , distill off the acetone, filter and distill. BP₁₄: 255–257°C., yield 13 g.
- To prepare diglycerol of undetermined configuration (ethers α - α ; - β , β - β), see also Wright and du Puis (1946).
- (XI) *3-aminopropane diol* (1,2): From glycide and ammonia (Knorr and Knorr, 1899).
- (XI & XII) *Mono- and diacetone glucose*: Prepared according to Bell (1935).

We have, then—excepting the last two—differently substituted derivatives of glycerol which in their physical properties are very closely related to glycerol itself (colorless, water-clear, viscous liquids which can easily be mixed with water). The two acetone compounds of glucose have been chosen because glucose represents the only compound that could replace in our previous experiments glycerol in the culture medium with no ill effects (Bloch, 1942). We experimented with the synthetically prepared glycerol to exclude any impurities in the natural glycerol.

For the following experiments, the compounds were dissolved, buffered and neutralized.

BACILLI

The strain used was of human type and highly virulent for guinea pigs. Bacilli were grown on a synthetic medium of the following composition: Ten to 14-day-old cultures were used.

NaH_2PO_4	3 g.
KH_2PO_4	4 g.
MgSO_4	2.5 g.
Sodium citrate.....	2.5 g.
Ferrous ammonium sulphate.....	0.01 g.
Glycine.....	5 g.
Glycerol.....	25 g.
Distilled water add 1,000 cc.	
pH adjusted to 7.0.	

METHODS

Respiration Experiments

Bacilli were filtered through paper (Whatman No. 5), thoroughly washed on the filter, suspended in distilled water and centrifuged at 3000 r.p.m. for fifteen minutes; this was repeated three times. The bacillary mass was then homogeneously resuspended in 0.06 M phosphate buffer pH 6.8 to make approximately 5 mg. dry weight of bacilli per cc. One cc. of this suspension was filled into each Warburg vessel, the total volume being 2 cc. + 0.2 cc. potassium hydroxide.

Temperature of the thermostate was 37.0° C. Gas used was oxygen. The respiration of the buffer-suspended bacilli in the absence of any nutrient served as control. Glycerol-promoted respiration was measured in every experiment, glycerol being added in a concentration of 0.2 Mol/l. When combined with glycerol, different compounds increased the Q_0 produced by this substance and gave thus an additional effect. As we showed in a previous paper (Bloch, 1944); the Q_0 produced by glycerol is to a large extent unaffected by the concentration of glycerol, so that an additional effect points to two separate and independent respiration mechanisms.

Growth Experiments

The compounds to be tested were added to the culture medium to replace glycerol; 50 cc. of culture medium (without glycerol) were filled into 200 cc. Erlenmeyer flasks and incubated from three to five weeks at 37° C.; the cultures were then filtered through paper, dried *in vacuo* and weighed. Our results are based on the average weight of at least three parallel flasks.

RESULTS

Respiration Experiments

(1) *Natural and synthetic glycerol*: No difference in the action of the two compounds on the respiration of tubercle bacilli can be seen. Both substances increase the oxygen uptake by 94 ± 5.75 per cent (average of 35 experiments). The relative increase depends on how intensively the bacteria were washed, as the maximum absolute value reached with glycerol is constant. The values to be compared must thus be based on experiments with bacilli that have passed through the same washings.

The oxygen consumption is of linear type during an experiment of six hours. Since the lag phase of *M. tuberculosis* is five to eight days, a bacillary multiplication cannot be expected during the short time of the experiment.

We found glycerol respiration to be independent of the acidity of the medium within a range of from pH 3 to 7, a fact already mentioned by Loebel, Shorr and Richardson in 1933.

(2) *Esters of glycerol*: The respiratory effect of the three esters of glycerol with acetic acid, that is, mono-, di- and triacetylglycerol, was investigated. If the respiration of tubercle bacilli is measured in different solutions of those esters in 0.06 M phosphate buffer pH 6.8, we find a considerable increase of oxygen uptake dependent on the concentration of the substrates (table 1). A characteristic experiment is presented in chart 1, from which two different facts appear:

(a) Unlike glycerol, with which the respiratory quotient is almost independent of concentration, we find in the case of glycerol esters for each compound a definite and characteristic optimum.

(b) The increase of the oxygen uptake produced by glycerol is considerably surpassed by that of glycerol esters. However, a combination of glycerol and glycerol esters does not produce an additional increase of respiration.

The question arose whether the glycerol esters are consumed as compound or

TABLE 1

The effect of various concentrations of mono-, di- and triacetyl glycerol upon the oxygen uptake of tubercle bacilli

CONCENTRATION	PER CENT INCREASE OF OXYGEN UPTAKE EFFECTED BY		
	Monoacetyl glycerol	Diacetyl glycerol	Triacetyl glycerol
Mol/l.			
0.5	206	38	14
0.166	400	161	129
0.14	428		
0.066		456	430
0.055	308	388	
0.05		346	440
0.033			480
0.025			398
0.022			390
0.018	200	211	246
0.006	119	132	152

Note: The average increase effected by glycerol from 0.5 to 0.01 M was 94 ± 5.75 per cent.

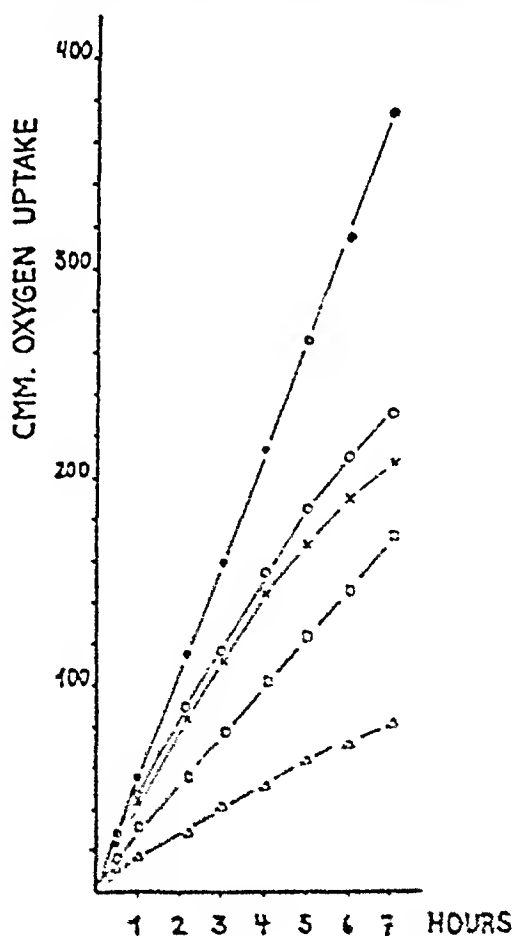


CHART 1. The effect of 0.2 Mol/l. of glycerol and of mono-, di- and triacetyl glycerol upon the oxygen uptake of tubercle bacilli.

- Monoacetyl glycerol.
 ○—○ Diacetyl glycerol.
 ×—× Triacetyl glycerol.
 □—□ Glycerol.
 △—△ Control.

whether they are split, so that the ester parts, that is, glycerol and acetic acid, are utilized separately. Tubercle bacilli are known to contain esterases (for references see Michaelis and Nakahara, 1923). We showed their activity by shaking equal quantities of bacilli in 0.2 M solutions of the different esters and titrating the resulting acetic acid with 0.1 n NaOH, using phenolphthaleine as indicator (table 2).

Moreover it is possible to show the esterase activity by the method of Rona and Lasnitzki (1924) in the Warburg apparatus, using a suspension of intact bacilli as well as cell-free extracts prepared by our method previously described

TABLE 2

The effect of the esterase of tubercle bacilli upon mono-, di- and triacetyl glycerol

TIME minutes	cc. 0.1 n NaOH		
	Monoacetyl glycerol	Diacetyl glycerol	Triacetyl glycerol
5	0.23	0.26	0.37
10	0.20	0.28	0.35
15	0.22	0.29	0.38
20	0.18	0.28	0.42
25	0.22	0.42	0.55
30	0.22	0.32	0.38
35	0.20	0.30	0.37
40	0.20	0.28	0.40
50	0.25	0.38	0.48
55	0.16	0.30	0.40
65	0.23	0.40	0.52
75	0.20	0.41	0.53
85	0.30	0.51	0.55
Total.....	2.81	4.45	5.70

Concentration of the substrates: 0.2 M, in a total amount of 50 cc. of distilled water. Temperature: 37° C. Titration with 0.1 n NaOH, with phenolphthalein as indicator. Enzyme preparation: 136 mg. (dry weight) bacilli per 50 cc. substrate solution. The spontaneous hydrolysis of the esters is insignificant under these conditions and can be neglected.

(Bloch and Suter, 1946). In the beginning, the reaction is a linear one; later, the curve grows more flat, yet without reaching an endpoint within twenty-four hours.

The acid quantity determined by titration is smaller than the theoretical value, owing to the fact that a part of the liberated acetic acid is oxidized by the tubercle bacilli (Cutinelli, 1940; Franke and Schillinger, 1944). As will be seen later, respiratory intensity depends on the concentration of the acetic acid present. It is obvious, therefore, that identical concentrations of the three esters are oxidized with different intensity. As shown in table 2, the bacillary enzyme liberates unequal quantities of acids within the same time unit. The optimum concentrations of mono-, di- and triacetyl glycerol, thus, vary from each other.

On the other hand, conclusions as to the actual concentration of acetic acid can be drawn from the concentration of an ester at the maximum oxidation rate. These values are displayed in table 1. They correspond to 10 to 15 per cent of theoretical values and are roughly the same as the values in table 2.

(3) *Glycerol ethers:*

(a) *Glycerol- α -monoisoamylether:* When dissolved at 0.06 Mol/l. in phosphate buffer, this compound exerts a similar effect on bacillary respiration as salicylate, benzaldehyde and other substances (Bernheim, 1941; Bloch, 1944), that is, in higher concentrations the oxygen uptake is completely inhibited, but, when the concentration is reduced, it rises to a maximum. A characteristic experiment is shown in chart 2.

After having seen in the case of esters that they are split by esterases and that the promoting respiratory effect can be attributed to the liberated acid compo-

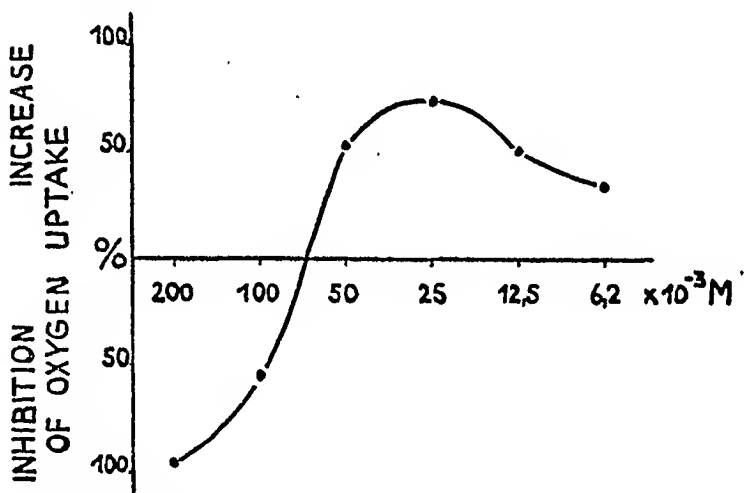


CHART 2. The effect of different amounts of isoamylic alcohol upon the oxygen uptake of tubercle bacilli.

nent, we suspected a similar behavior in the present case and tried to prove that the ether, too, can be split.

Bernheim (1941) showed that isoamylalcohol increases the oxygen consumption of tubercle bacilli. We could confirm this fact and found in addition that the respiratory rate of the ether depends on concentration just as that for the acetic acid does (see later). Identical inhibitory or promoting effects can be seen with isoamylalcohol solutions one-half to one-third as concentrated as the corresponding molar concentrations of the alcohol-glycerol-ether. This relation depends on the speed of the splitting reaction, due to the fact that only the liberated alcohol is oxidized. In one point, however, this case differs from the experiments with acetic acid or glycerol-acetic acid-esters: the oxygen uptake reached with glycerol is nowhere surpassed. According to this, the combination of glycerol with isoamylalcohol does not produce any additional effect.

(b) *Glycerol- α -monomethylether:* This compound does not exert any effect on

bacillary respiration within the limits of 0.2 to 0.001,25 Mol/l. Methanol is equally ineffective. Thus, we cannot affirm that this ether is split. We rather think it is not, otherwise the liberated glycerol should affect the oxygen consumption of the bacilli.

(e) α - α -diglycerol ether: This compound does not exert any inhibitory effect. The oxygen uptake is slightly increased to about 50 per cent of the glycerol effect with concentrations of 0.4 to 0.2 Mol/l. The increase being no greater, the ether does not seem to split and the entire compound is probably used as substrate.

(d) *Acetone glycerol*: This substance also increases the oxygen uptake, but less than glycerol. As in the previous case, we think that no splitting takes place, and this for two reasons: (1) after shaking bacillary suspensions with acetone glycerol, even for many hours, we were unable to detect any traces of acetone; (2) as seen in table 3, acetone when used separately exerts an inhibitory effect

TABLE 3

The effect of glycerol, acetone, and acetone glycerol upon the oxygen uptake of tubercle bacilli

SUBSTRATE	INCREASE (+) OR INHIBITION (-) OF OXYGEN UPTAKE
	<i>per cent</i>
—	± 0
Glycerol 0.2 M.....	+94
Acetone glycerol 0.2 M.....	+96
Acetone glycerol 0.05 M.....	+64
Acetone glycerol 0.0125 M.....	± 0
Acetone 0.2 M.....	-98
Acetone 0.0125 M.....	-44

on the oxidation rate. From the lack of a similar decrease, when the compound is used as a whole, we conclude that no acetone is liberated.

(e) *Mono- and diacetone glucose*: Unlike the corresponding glycerol compound, these substances are not utilized at all and so do not produce any effect, neither increasing nor reducing the respiration rate.

(4) *Other compounds*:

(a) *C-methylglycerol*: This substance, produced entirely synthetically, has the same effect on cell respiration as glycerol itself.

(b) *3-aminopropane diol*: This compound gives a strong basic reaction (pH of the 0.2 M solution in water: 10.25). Owing to this fact, respiration is inhibited. However, if neutralized, the substance exerts a slight increasing effect (25 per cent more than control with 0.2 Mol/l.).

(c) *Acetic acid*: This substance, too, has to be neutralized, as the increase of respiration produced by acetic acid depends on pH. An optimum appears at pH 6.1 (see chart 3). This behavior differs entirely from that of glycerol. A similar statement was made by Loebel, Shorr and Richardson (1933) when they used lactic acid and glycerol.

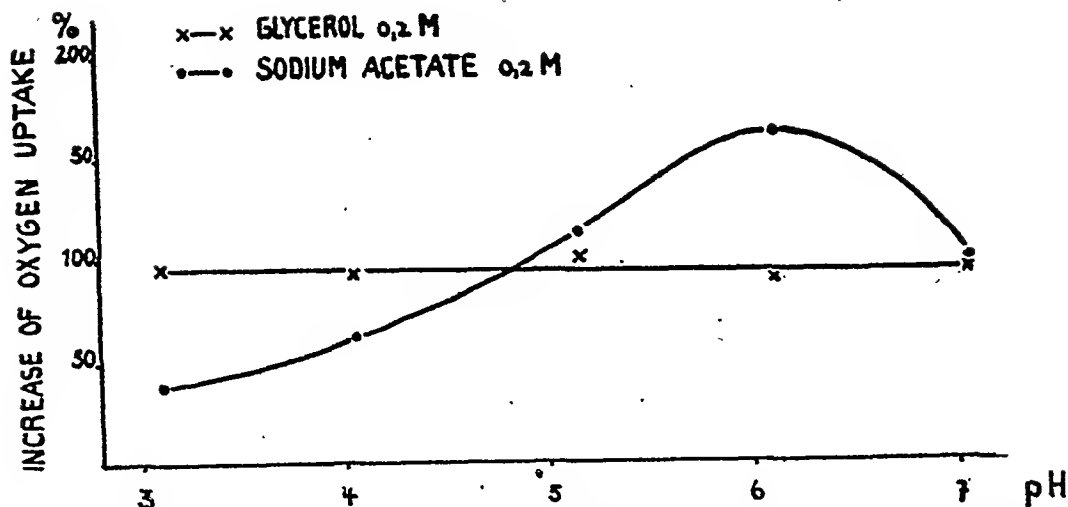


CHART 3. The oxygen uptake of tubercle bacilli with glycerol and sodium acetate at different pH values of the medium.

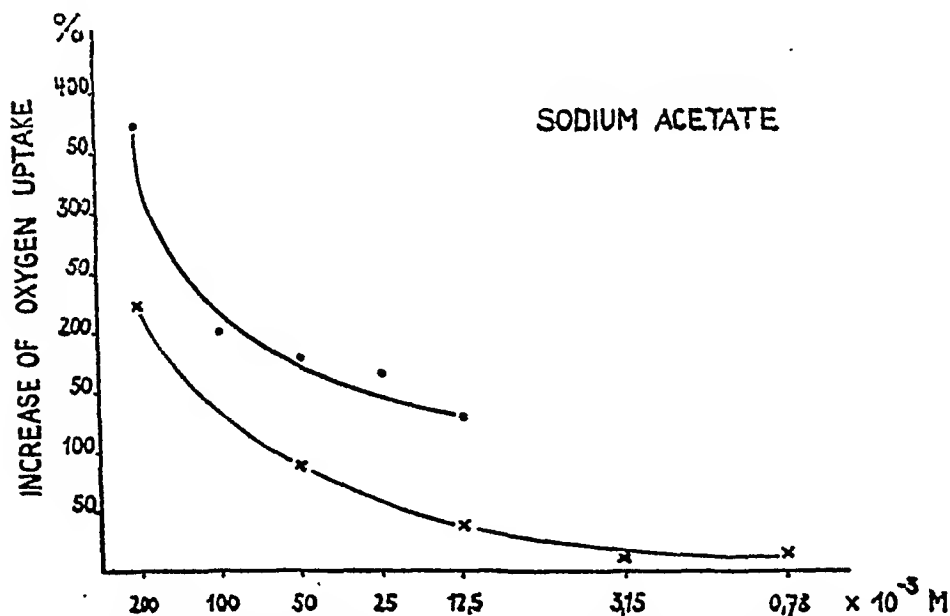


CHART 4. The effect of various concentrations of sodium acetate upon the oxygen uptake of tubercle bacilli. The two curves represent two experiments with different amounts of bacteria.

×—×: 4.7 mg. dry weight of bacteria in each Warburg-vessel.

●—●: 8.3 mg. dry weight of bacteria in each Warburg-vessel.

Moreover, the respiratory rate depends on concentration of neutralized acetic acid (or sodium acetate) and rises with the concentration of the substrate (chart 4). This behavior, too, is different from that of glycerol (Bloch, 1944).

The addition of 0.01 M KCN gives an inhibition up to 60 per cent for acetate, and less than 30 per cent for glycerol.

There are, thus, three points where glycerol and acetate respiration differ from each other: dependence on pH, dependence on concentration and inhibition by KCN. We conclude from these facts that two enzyme-systems, belonging to different types, are acting in respiration in the presence of glycerol and of acetic acid, a conclusion which is further supported by the fact that the increases in oxygen uptake due to the two substances are added one to another when optimum concentrations are combined (0.025 M for acetate; 0.2 M for glycerol).

The dependence on pH of respiration in the presence of acetate also gives an easy explanation for the concentration optima observed in the case of glycerol esters, the liberated acetic acid producing even in buffered solutions an unfavorable pH for the respiration of the microorganisms, and, thus, a concentration proves most effective that does not correspond to the real optimum concentration found in neutralized solutions.

Growth Experiments

(1) *Effect of substances increasing the respiration rate:* It has already been described in a previous communication (Bloch, 1946) that there is no parallelism between the promoting effect of a substance on respiration and on growth of *M. tuberculosis*. Nevertheless, in substances so closely related to glycerol, we expected to find a more corresponding behavior. As will be seen, this supposition proved wrong.

Substances to be tested were added to culture media in concentrations corresponding to glycerol, that is, 0.2 Mol/l. The media used were the following:

- (a) Synthetic medium without glycerol.
- (b) Synthetic medium without glycerol + 2 per cent normal human serum.
- (c) Nutrient broth agar.
- (d) Nutrient broth agar + 10 per cent normal horse serum.

The bacilli grown as control cultures on synthetic medium with glycerol gave in 65 experiments an average dry weight of 227.5 ± 22.3 mg. Each determination is based on the average weight of three culture flasks.

The results of these experiments show that none of the substances tested is able to replace glycerol, even to a moderate degree. The addition of substances known to promote growth, such as blood and serum, does not affect the result.

DISCUSSION

A comparison between the results of the respiration and of the growth experiments will once more confirm the fact that the action of a substance on the respiration and the action on the growth of tubercle bacilli is of a completely different order. The effects are totally dissimilar. This lack of parallelism appears to us especially impressive in the present case, because glycerol and the majority of the compounds tested are chemically so closely related. Kondo (1925) reported an experiment in which tubercle bacilli were able to grow with

acetic acid as the only source of carbon. The strain used in our experiments did not utilize acetate as nutrient, although its ability to use it for its respiratory metabolism was very marked. The lack of similarity mentioned above is even more striking in the case of methylglycerol and diglycerol ether, two compounds very similar to glycerol itself. The properties required in a substance that is to act as a growth-promoting factor seem, therefore, to be much more closely defined than those required in substances that increase respiration. A large number of different compounds are known which are able to increase the oxygen uptake of tubercle bacilli but only a few growth-promoting substances. With regard to inhibitory substances this relation is in one sense just inverted: we know a lot of compounds with inhibitory action on growth, but only a few acting as respiratory inhibitors (Bloch, 1946).

These facts confirm the finding that respiration and multiplication of the cell are two entirely different mechanisms connected only in one point: multiplication depends on an intact respiratory system, whereas respiration can function even if the multiplication apparatus is blocked. Therefore, the mechanism of multiplication seems to be more specific than the system controlling respiration: its chemical differentiating power is a better one, as demonstrated by the small number of substances acting as nutrients; its function is more sensitive and therefore easier to disturb, as shown by the comparatively important number of growth-inhibiting substances.

Apparently different experiments have led to the same conclusions concerning the character of cell growth and multiplication of *M. tuberculosis*. However, as shown by Sevag (1944), these findings may be essentially the same when we come to microorganisms other than tubercle bacilli. Yet there is one difference: accessory growth factors which play an important part in growth experiments with other microorganisms are not known to affect *M. tuberculosis*. The experiments with synthetic glycerol have not suggested an eventual importance of similar still unknown substances. Nevertheless the findings of Drea (1942, 1944) must be taken into account; even with all possible precautions the necessary quantity of the inoculum is still considerable as compared with that of other microorganisms. We cannot, in any event, exclude the action of accessory growth factors that are, so far, unknown.

Our experiments do not explain the nature of the extraordinary part played by glycerol as nutrient in the metabolism of *M. tuberculosis*, but they rather confirm it, showing the specificity of this compound when compared with the action of chemically closely related substances.

SUMMARY

1. The influence of 12 different compounds, chemically related to glycerol, upon the respiratory metabolism and the growth of tubercle bacilli was investigated. The majority of the substances increased the oxygen uptake of the bacilli, but none was able to replace glycerol as nutrient in a synthetic medium.

2. Several esters and ethers can be split by an enzymatic action of the bacilli and their liberated constituents further utilized in the bacterial metabolism.

3. Many substances of different chemical nature are able to increase the oxygen uptake of tubercle bacilli, but this action often depends on the concentration of the substances and the pH of the medium, whereas glycerol was found to be much less affected by these factors.

4. Additional effects on the bacterial respiration can be seen if glycerol is combined with acetic acid, but not with isoamylic alcohol, although both acetic acid and isoamylic alcohol increase the oxygen consumption of the bacilli. From this fact it can be concluded that the oxygen consumption of tubercle bacilli may be based on different respiratory mechanisms.

5. The results of the experiments confirm that respiration and growth depend on two different metabolic systems. The latter seems to be more specific as to the metabolites which can be utilized.

SUMARIO

1. Investigóse el influjo de 12 distintos compuestos, químicamente enlazados con el glicerol, sobre el metabolismo respiratorio y la proliferación de los bacilos tuberculosos. La mayoría de las sustancias acrecentaron la absorción de oxígeno por los bacilos, pero ninguna pudo suplantar al glicerol como nutriente en un medio sintético.

2. Mediante una acción enzimática de los bacilos, pueden disolverse varios ésteres y éteres, y utilizarse ulteriormente sus componentes liberados en el metabolismo bacteriano.

3. Muchas sustancias de diversa naturaleza química pueden reforzar la absorción de oxígeno por los bacilos tuberculosos, pero esa acción depende a menudo de la concentración de las sustancias y del pH del medio, en tanto que el glicerol se vió mucho menos afectado por dichos factores.

4. Pueden observarse nuevos efectos sobre la respiración bacteriana si se combina el glicerol con ácido acético, pero no con alcohol isoamílico, aunque tanto el ácido como el alcohol acrecientan el consumo de oxígeno de los bacilos, de lo cual cabe deducir que el consumo de oxígeno por los bacilos tuberculosos puede basarse en distintos mecanismos respiratorios.

5. El resultado de los experimentos confirma que la respiración y el crecimiento dependen de dos distintos sistemas metabólicos, pareciendo el último más específico en cuanto a los metabolitos utilizables.

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INFLUENCE OF SULFASUXIDINE AND SUCCINIC ACID UPON THE TUBERCLE BACILLUS¹

MICHELE GERUNDO²

The observations described in this paper were made in the course of some experimental work which was carried out in an attempt to ascertain whether sulfasuxidine had any bacteriostatic action upon *Mycobacterium tuberculosis*. It was assumed that slow growing bacteria would be more easily influenced by sulfonamides inasmuch as the drug would inhibit growth or division of cells before it begins. Previous experiments had shown that sulfathiazole inhibits the growth of the bacilli *in vitro*. Six different strains of *M. tuberculosis* were used in the experiments, 3 of them being chromogenic varieties.

Incidentally, when culture was carried on bouillon-glycerol, in presence of sulfasuxidine, the pellicle fell rapidly to the bottom and grew alongside the walls of the tube. Microscopic examination revealed long granular rods and beaded forms in the culture tubes containing sulfasuxidine, whereas it showed only short plump rods in the controls.

The addition of para-aminobenzoic acid stimulated growth and pigment production in all the strains with the exception of one which showed growth in the tube containing sulfasuxidine but no growth in the presence of para-aminobenzoic acid alone.

In order to avoid the influence of any substance which could be considered antagonistic to sulfonamides, Long's synthetic medium was chosen. The bacillus grows very slowly in this medium and usually only when heavy inoculum is used. Six tubes were inoculated for each strain used.

Much to our surprise the growth was abundant in tubes containing sulfasuxidine and still better when sulfasuxidine and para-aminobenzoic acids were present in the same tubes. Para-aminobenzoic acid alone did not stimulate such abundant growth as when it was combined with sulfasuxidine, but production of pigment was definitely more abundant in its presence. Whether it played a rôle in the formation of pigment is not clear, as even strains which did not form pigment on ordinary media formed pigment in its presence.

It was assumed that probably growth in the presence of sulfasuxidine was due to the succinic acid radical present in the drug. Such hypothesis was based on the knowledge that asparagine, which is necessary in the synthetic medium to support growth, is metabolized by the bacteria to succinic acid, and utilized as such as a source of energy for growth.

Long (6) in his work on the metabolism of the tubercle bacillus had already found that ammonium salts of dibasic acids supported good growth. Ammonium succinate and the ammonium salts of malic and tartaric acids, which are hydroxy acids from succinic acid, were found to be good substrates for the growth of the bacillus. By clever intuition he anticipated that the metabolism of the

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tubercle bacillus may follow a path—perhaps identical with what is now known as the Szent-György or Krebs cycle—in which succinic acid is an important link in the chain.

In consequence, sodium succinate and para-aminobenzoic acid were added to the medium containing asparagine. The growth was more abundant than in tubes without succinate, but the rôle of para-aminobenzoic acid was not clearly established, as its addition did not appear to be essential for the development of the bacteria.

Finally, asparagine was excluded entirely and Long's medium was modified as follows:

Ammonium citrate	10 g.
Potassium acid phosphate	3 g.
Sodium carbonate, anhydrous	3 g.
Sodium chloride	2 g.
Magnesium sulphate	1 g.
Ferric ammonium citrate	0.05 g.
Sodium succinate	10 g.
Glycerol	50 g.
Water to 1000 cc.	
5 cc. of a 1:1000 solution of para-aminobenzoic acid was added for every 100 cc. of medium.	

In this medium the growth of mycobacteria was more abundant than in ordinary Long's medium and to a certain extent more rapid. There was no difficulty for successive transplants in this medium. Para-aminobenzoic acid was not essential to growth, as its rôle was apparently concerned only with the production of pigment.

Table 1 summarizes the results of the various cultures carried out on the original Long's medium and on its modified form. It is seen from it that Long's medium without asparagine is unable to support growth, but its modified form with sodium succinate gave more abundant growth than the original medium.

It is rather difficult to formulate a clear idea of the action of sulfonamides upon tubercle bacilli. *A priori*, given the nonspecific action of sulfonamides upon bacteria, it should not be surprising that they do exert a bacteriostatic influence upon the bacterium. Assuming that sulfonamides inhibit growth and division (and there is an extensive literature to prove it) the tubercle bacillus should be suitable for experimentation, because of its very slow growth. Fitzgerald and Feinstone (1), in correlating the antibacterial activity of sulfonamides with their acid dissociation constants and their ability to withstand the inhibitory action of para-aminobenzoic acid, extended the theory of non-specificity of sulfonamides to include their effect on the tubercle bacillus.

Bazzicalupo (2) noted that sulfonamide at a concentration of 8 mg. per cent had bacteriostatic effect upon the tubercle bacillus.

Even in the experimental therapeutic field Greey, Campbell and Culley (3) obtained good results with sulfanilamide in experimental tuberculosis of the guinea pig, if given early before spreading began. Other authors have obtained similar results with various compounds.

Mayer (4) has described a yellow pigment formed by a special strain of *Mycobacterium tuberculosis*, var. *hom.*, in the presence of para-aminobenzoic acid or procaine. The formation of this pigment involves a specific oxidase; the pigment is an unstable product of para-aminobenzoic acid and contains oxidized NH_2 groups. He found that 1:1000 sulfanilamide completely inhibited growth of the bacilli. When para-aminobenzoic acid was added, then sulfanilamide in various concentrations either inhibited completely or decreased the formation of the yellow pigment. The inhibition may be due to inactivation of an essential metabolite as the result of reaction between sulfonamide and para-aminobenzoic acid, but it seems more likely that it is of enzymatic nature, the sulfonamide directly poisoning the enzyme.

TABLE 1
Growth of tubercle bacilli on modified Long's media

*STRAINS OF TUBERCLE BACILLI:	A	B	C	D	E	F
Long's medium.....	+	+	+	+	+	+
Long's medium without asparagine.....	?	-	-	-	-	-
Long's medium with sulfasuxidine.....	+±	+±	+	+	+	+±
Long's medium with sulfasuxidine and para-aminobenzoic acid.....	+†	++	+	+	+	++
Long's medium with para-aminobenzoic acid....	+±	+±	+	+	+	+
Long's medium with sodium succinate.....	++	†+	+±	†±	+±	++
Long's medium with sodium succinate and para-aminobenzoic acid.....	++	++	+±	+±	+±	++
Modified Long's medium with sodium succinate..	++	++	+±	+±	+±	++
Modified Long's medium with sodium succinate and para-aminobenzoic acid.....	†+	++	+±	+±	+±	++

* All the strains were isolated from human cases except F which was furnished by Ely Lilly and Company.

Our results with sulfasuxidine are at variance with those of the authors already mentioned and with our previous tests with sulfathiazole. It is true that an action exercised by one sulfonamide must not be entirely similar to that of any other sulfonamide; in this respect, results are not strictly comparable. In using a conjugated sulfonamide, succinyl-sulfathiazole, growth was definitely more luxuriant in presence of the drug than on ordinary Long's medium. That the tubercle bacillus is capable of utilizing succinic acid as a substrate is already well known; its ability to grow on Long's medium very likely is due to the fact that the medium contains asparagine, which is broken down to succinic acid, and glycerol, which may also form succinic acid under certain conditions (5). The chromogenic strains used in our experiments, produced pigment in presence of para-aminobenzoic acid alone or combined with sulfasuxidine; there was actually no interference or antagonism.

The substitution of asparagine with succinic acid alone or combined with para-aminobenzoic acid proves in our experiments definitely that the tubercle bacillus is capable of utilizing this acid as a substrate. The rôle of asparagine may be explained by the fact that succinic acid which is a structural part of

both amide-N and amino-N is the real factor in the acceleration of bacterial growth.

SUMMARY

The addition of sulfasuxidine to bouillon-glycerol did not inhibit the growth of the tubercle bacillus, but induced development of long granular rods and beaded forms.

When Long's synthetic medium was used, the bacteria grew more abundantly in the tubes containing sulfasuxidine, either alone or with para-aminobenzoic acid.

On the assumption that the succinic acid radical present in sulfasuxidine was the factor stimulating growth, the bacteria were cultured in a modified synthetic medium, in which sodium succinate was substituted for asparagine; this modified form supported better growth than the original medium.

It seems reasonable to conclude that asparagine is not necessary for growth as a source of amide-nitrogen and amino-nitrogen and that succinic acid, which is the structural element of both forms of nitrogen, is the factor involved in the development of the bacterium. Para-aminobenzoic acid was not essential for growth, but its rôle was concerned with the formation of pigment.

SUMARIO

Cultivo del Bacilo Tuberculoso

La adición de sulfasuccidina al caldo-glicerina no inhibió el crecimiento del bacilo tuberculoso, pero sí hizo proliferar bastoncillos granulares largos y cuerpillos moniliformes.

Al emplear el medio sintético de Long, las bacterias se desarrollaron con mayor abundancia en los tubos que contenían sulfasuccidina, ya sola o combinada con ácido para-aminobenzoico.

Partiendo de la suposición de que el radical de ácido succínico presente en la sulfasuccidina era factor estimulador del desarrollo, las bacterias fueron cultivadas en un medio sintético modificado, en el cual se empleó succinato de sodio en vez de asparagina; esta fórmula modificada mostró un desarrollo mejor que el medio primitivo.

Parece lógico deducir que la asparagina no es necesaria para el desarrollo como fuente de amido-nitrógeno y amino-nitrógeno, y que el ácido succínico, que es el elemento estructural de ambas formas de nitrógeno, es el factor que interviene en el desarrollo de la bacteria. El ácido para-aminobenzoico no fué esencial para el desarrollo, pero sí intervino en la pigmentogenia.

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CULTIVATION OF TUBERCLE BACILLI FROM GASTRIC JUICE¹

A Study of the Factors Affecting the Cultivation of *Mycobacterium tuberculosis* from Gastric Juice

VERA VINCENT AND EDWARD A. BIRGE

During the past fifteen years many authors have shown that aspiration of the contents of the fasting stomach is a practical method for the diagnosis of tuberculosis in children and in patients producing scanty amounts of sputum. Recently, however, several papers have appeared which cast serious doubt upon the value of this diagnostic procedure when cultures are not made immediately after the specimen is collected.

Originally described by Meunier in 1898 (1), diagnostic gastric lavage was reintroduced by Armand-Delille (1a) in 1927. At first only smears, made after digestion and concentration of the stomach contents, were employed. Later, Poulsen *et al.* (6) used guinea pig inoculations and cultures to make the method more sensitive. Examination of the early literature fails to show that anyone carried out experiments to determine the possible effect of gastric juice on the tubercle bacillus. It was generally believed that acid had little effect on the viability of the bacillus although the literature did not justify this assumption. In 1889 Straus and Wurtz (10) reported that, although the gastric juice of dogs would not destroy tubercle bacilli after contact for one to six hours, contact for eight to twelve hours would produce some attenuation of the organisms' virulence for guinea pigs, while an exposure of eighteen to thirty-six hours killed the organisms. Inkster and Gloyne (3) showed that tubercle bacilli would retain their virulence for guinea pigs after exposure to normal gastric juice for two hours, but they did not study the effect of a longer period of time. Roper and Ordway (7), in contrast to most of the workers, stated that tubercle bacilli were only slightly inhibited by contact with one-tenth normal hydrochloric acid for four days. Details of the experiment are not given. Floyd and Page (2) suspended tubercle bacilli in an artificial gastric juice for periods varying from three to twelve hours. The suspensions were kept at incubator temperature and subsequently guinea pigs were inoculated. A three-hour exposure had no effect on the bacilli, but exposure to the gastric juice for six and twelve hours produced a marked lessening of the number of lesions found in the animals. Exposure to filtered duodenal contents had no effect on the virulence of the organisms.

Recently, Schwarting (8) has reported that placing gastric aspirations in the ice box or allowing them to stand at room temperature for one to two days produces a considerable number of false negative reports. She is inclined to attribute this result to the presence of an inhibitory substance, described by Piasecka-Zeyland (5), in the saliva swallowed during the passage of the stomach tube. Kramer (4) mixed heavily positive sputa with normal gastric juice and incubated the mixture at 37°C. for varying periods of time. The tubercle

¹ From the Wisconsin State Laboratory of Hygiene, Madison, Wisconsin.

bacilli were able to withstand this treatment for ten hours, but after twenty-one hours the mixture was no longer pathogenic for guinea pigs. He assumed that gastric lipase or pepsin was responsible for killing the organisms. Sprick and Towey (9) divided 33 gastric aspirations into three equal parts. One portion was cultured and inoculated into a guinea pig at once, the second and third portions were allowed to stand at room temperature for twenty-four and forty-eight hours, respectively, and then treated in the same manner as the first portion. Seventy-three per cent of the specimens examined immediately were positive by one or the other method, 45 per cent were positive after standing for twenty-four hours, while only 21 per cent were positive after standing for forty-eight hours.

For many years this laboratory has been receiving gastric aspirations for the diagnosis of tuberculosis from most of the sanatoria in Wisconsin as well as from many general hospitals and private doctors. These specimens represent both single aspirations and three-day poolings. Allowing for twenty-four to forty-eight hours in transit, our specimens are two to five days old by the time they arrive at the laboratory. The appearance of these recent papers demonstrating the fact that a high percentage of false negatives may occur when gastric aspirations are allowed to stand was disturbing. Accordingly, we have undertaken a study to determine the nature of this inhibitory substance and to determine what corrective measures could be applied to counteract it.

MATERIALS AND METHODS

Two types of specimens were employed—gastric aspirations from known tuberculous patients and normal gastric juice seeded with cultures of tubercle bacilli freshly isolated from sputa or spinal fluids. No organisms obtained by culture of gastric contents were used for seeding in order to eliminate any possibility of strain adaptation to gastric juice. These experimental specimens were handled in the same way as our routine specimens. They were concentrated by sodium hydroxide digestion with subsequent centrifugation and neutralization. The entire sediment was distributed over the surface of one tube of Hohn's and one of Petragnani's medium. No guinea pigs were inoculated, since unpublished data in our laboratory as well as many papers in the literature show that approximately the same number of positives are obtained by each method. The cultures reported as positive all had the colony appearance typical of *M. tuberculosis*.

EXPERIMENTAL

The pH of 799 routine gastric aspirations received from all over the state was determined by means of thymol blue and methyl orange indicators supplemented by nitrazine paper. The range of pH values was found to vary from 2 to 8. No specimen had a pH value above 8.5. A small number of specimens were more acid than pH 2, but we had no practical method of determining pH values in this range. Pepsin was determined on many of these specimens by Nirenstein and Schiff's modification of Mett's method (11). We found that a low pH was invariably associated with large amounts of pepsin while specimens which were neutral either had no pepsin or a very negligible amount. There was no correla-

TABLE 1
Percentage of positive cultures obtained from routine gastric aspirations

pH OF SPECIMEN	NUMBER OF SPECIMENS	PER CENT POSITIVE CULTURES	PER CENT CONTAMINATED CULTURES
2	90	1.1	6.7
2.5	61	1.6	0
3	100	4	2
4	78	7.8	1.3
4.5	45	6.6	2.2
5	103	3.9	4.9
6	57	12.3	8.8
7	126	16.7	13.5
7.5	74	14.9	19.0
8	65	9.2	21.5

TABLE 2
Effect of pH on the survival of tubercle bacilli in vitro

NUMBER	BACILLI SUSPENDED IN	SUSPENSION KEPT AT	IMMEDIATE CULTURE	SUBSEQUENT CULTURES IN DAYS						
				1	2	3	4	5	6	7
71621	Broth, pH 2.5	Room temperature	+++*	+	—	—	—			
			33	32						
73089			++++	+++	+++	++	+			
			29	29	29	29	35			
67607	Buffer, pH 2.5	Ice box	++++		+		—			
			18		39					
65212			++++		++++		—			
			28		26					
67644			++++		++		—			
			18		33					
73088	Broth, pH 6.2	Room temperature	+++	+++	+++	+++	+++			
			29	28	27	26	25			
71620			++++	++++	++++	++	+			
			24	23	22	32	31			
67607	Buffer, pH 6.2	Ice box	++++		++++		++++			++
			18		25		23			20
65212			++++		++++		++++			++++
			18		26		37			35
67644			++++		++++			++++		
			25		23			20		

* Arabic numerals designate day growth was first observed.

Plus signs indicate average amount of growth on 2 tubes of media:

- + 1 to 15 colonies
- ++ 15 to 30 colonies
- +++ 30 to 50 colonies
- ++++ over 50 colonies

tion between the amount of mucus in the specimen and the results of the culture. Reference to table 1 will illustrate the relation between the acidity of the specimen and the number of positive cultures obtained. The presence of a pH lower than 6 apparently renders the specimen useless if it has stood for any length of time. These routine gastric aspirations represent specimens obtained from persons with incipient tuberculosis or from patients convalescent at the various sanatoria or rest camps, so that a high percentage of positive cultures is not to be expected. One complication found in this study is the increased percentage of contaminations which occur as the pH of the specimen increases.

Suspensions of tubercle bacilli were made in a phthalate-HCl buffer rendered isotonic with 0.5 per cent saline and in tryptone broth. The acidity of both

TABLE 3
Influence of pH and environment on cultures made from gastric aspirations

pH OF SPECIMEN	NUMBER OF SPECIMENS	SECOND PORTION HELD	GROWTH OF SECOND CULTURE		
			Same amount as original culture	Diminished	None
6 or above	5	Ice box 3-4 days	4	0	1
4-6	9		7	2	0
below 4	8		2	3	3
6 or above	3	Room temperature 3 days	1	0	2
4-6	1		0	0	1
below 4	9		0	1	8
6 or above	5	Ice box 3 days then Room temperature 2 days	3	2	0
4-6	8		0	0	8
below 4	8		0	1	7

suspending media was adjusted to pH values of 2.5 or 6.2. These suspensions were heavy enough so that a loopful of the mixture gave an abundant growth on the culture media used. Table 2 illustrates the results which were obtained. Fairly rapid killing of the organisms, as measured by the amount of growth on cultures, occurred in the acid specimens, but the number of bacilli failed to decrease greatly when a neutral suspending fluid was used. The temperature at which the suspensions were kept played little part in determining the length of survival.

A series of artificially inoculated, normal gastric aspirations and gastric aspirations from tuberculous patients were also examined. These specimens, regardless of origin, were thoroughly mixed by shaking by hand and then divided into two parts. The first portion was cultured at once. The second portions were cultured either after standing at room temperature for three days, after being in the ice box for three days or after being placed in the ice box for three days plus two days at room temperature for a total of five days. In addition, 3 specimens

TABLE 4
Effect of preliminary neutralization on cultures

SPECIMEN	PEPSIN VALUES	IMMEDIATE CULTURE	SECONDARY CULTURES†	
			pH 6.5-7.0	pH 2.0-3.0
66735	1064	++++* 27	++++ 31	+ 42
82185	400	++++ 36	+ 56	—
87204	0	+ 48	—	—
87701	256	++++ 23	+ 23	—
88559	324	++++ 21	+ 30	—
89186	324	+ 44	+ 44	—
91186	256	++ 47	++ 35	—
91187	256	++++ 29	++++ 35	1 col.* 49
91188	144	+++ 29	++++ 24	1 col.* 42
91890	450	+++ 38	—	—
91891	635	++++ 27	+++ 34	—
94352	1124	1 col.‡ 40	—	—
94896	0	—	+ 33	—
94897	400	++ 46	+ 48	—

* See table 2.

† Secondary cultures made after standing in ice box for two days, then in room temperature for three days.

‡ One tube only showed a single tuberculosis colony.

were divided into two parts and both cultured at once; these specimens gave identical results with both cultures. Table 3 shows the results of this experiment. The detrimental effect of high acidity is clearly evident. Storage at ice box temperatures apparently slows the process somewhat. With a few neutralized specimens we found that there was no difference between the first and second cultures, even when the second portion was allowed to stand in the ice box for five days before cultures were made.

Finally, 14 gastric aspirations were divided into three equal parts. One portion was cultured at once. The second portion was brought to a pH of 2 to 3, by means of hydrochloric acid if necessary, while the third portion was brought

TABLE 5
Effect of pepsin on vivability of tubercle bacilli

CULTURE	AMOUNT PEPSIN	SUSPENSION KEPT IN	IMMEDIATE CULTURE	SECOND CULTURE-DAYS	
				2	5
64018	256	Ice box	++++* 42	++++ 40	++ 40
85451	538		++++ 30	++++ 36	++ 37
67068	1024		++++ 25		+ 37
64018	256	Room temperature	++++ 42	++++ 40	+ 36
85451	538		++++ 30	+ 40	—
67068	1024		++++ 25		+ 37

* See table 2.

to a pH of 6.5 to 7.0 by the use of sterile one-tenth normal sodium hydroxide, if necessary. The second and third portions were then placed in the ice box for two days plus three days at room temperature for a total of five days after which they were concentrated and cultured as usual. This time interval was chosen in order to simulate the conditions under which we receive the majority of our specimens. Table 4 gives the experimental details. The neutral portion of the gastric specimen clearly gives better results than the acid portion.

This last experiment indicates that the pepsin content of the specimen plays only a secondary rôle in determining the survival of tubercle bacilli. This was confirmed by suspending tubercle bacilli in saline to which varying amounts of dried pepsin were added. The pepsin activity was determined by the egg-white digestion technique mentioned previously. Table 5 indicates that the survival

of the organisms over a five-day interval of time was fairly satisfactory. The pH of these suspensions varied between 5 and 6.

DISCUSSION

The experimental work reported in this paper points to only one conclusion. The tubercle bacillus, although it is amazingly resistant to high degrees of acidity, is not able to withstand contact with hydrochloric acid indefinitely. Survival of the bacilli in the stomach contents depends on the amount of free acid present in the specimen. The length of survival in an acid medium, however, can be modified by the temperature at which the specimen is kept. Since the destructive process is slowed in the cold, we believe that pepsin digestion in an acid medium hastens the killing of the bacilli when the specimen is allowed to stand at room temperature. Strain variation in respect to acid resistance has not been studied.

The experimental evidence also shows that in neutral gastric juice the tubercle bacillus will usually survive for at least five days. Here again survival is best at refrigerator temperatures although the difference is less marked. The occasional poor results are probably due to the killing of the tubercle bacillus by other bacteria or by the process of concentration. The latter supposition is the most likely.

It is obvious that the techniques now in general use must be modified if we are not to obtain a large number of false negative reports. Prompt culturing of the specimen after it is collected would be ideal. Local laboratory conditions, however, will modify this ideal arrangement because of shortages of personnel and money. Few laboratories are able to double or triple their work in order to make separate daily cultures in place of a single culture of a two- or three-day gastric pooling. The necessity of multiple cultures or pooling is illustrated by the fact that in the course of this study 21 patients on the tuberculosis service had gastric lavages on two or three successive days. Each aspiration was cultured separately as soon as it reached the laboratory. Ten patients were consistently negative, 8 were consistently positive, while in 3 cases both positive and negative cultures were obtained.

It is our belief that for practical purposes gastric aspirations may still be collected and pooled over a period of two or three days if the specimen is kept in the ice box continuously and if the pH of the specimen is brought to approximate neutrality. Reference to table 1 shows that preliminary neutralization is not without its drawbacks. As the pH of the specimen increases, the number of positive cultures also increases, but the incidence of contaminated cultures increases at the same time. These contaminations are due to the rapid growth of bacteria, especially spore forming bacilli and fungi, during the period that the specimen stands. These bacteria cannot be entirely eliminated by the sodium hydroxide digestion because the prolonged contact with strong alkali necessary for their destruction will also kill the tubercle bacillus. Ordinarily, most of this contaminating growth is held in check by the acidity of the specimen. Where the specimen can be continuously refrigerated, preliminary neutralization to a pH

value of 6.5 to 7.0 is the best procedure. However, where specimens are sent to a central laboratory or must stand at room temperature for several hours, we feel that the pH should only be brought to about 6.0. The difference in the number of positive cultures obtained at this pH as compared with the number obtained with specimens at a pH of 7 is small, but the percentage of contaminated cultures is definitely less at the lower pH. When specimens are sent to a central laboratory, it will probably be impossible to avoid false negative cultures, but preliminary neutralization of the specimen prior to mailing should improve the results obtained.

SUMMARY

1. A study has been made to ascertain the factors which influence the survival of tubercle bacilli in gastric juice.
2. Survival of the tubercle bacillus depends on the acidity of the gastric juice. The more acid the specimen, the shorter is the survival time.
3. To eliminate false negative reports, gastric specimens should be examined immediately either by cultures or by guinea pig inoculation.
4. Neutralization of gastric specimens will allow the tubercle bacillus to live several days if the specimens cannot be examined at once.

SUMARIO

1. En este estudio tratóse de averiguar qué factores afectan la sobrevivencia de los bacilos tuberculosos en el jugo gástrico.
2. La sobrevivencia del bacilo tuberculoso depende de la acidez del jugo gástrico: mientras más ácido el ejemplar, menor la duración de la sobrevivencia.
3. A fin de eliminar enfermos seudonegativos, hay que examinar los ejemplares gástricos inmediatamente, bien por medio de cultivos o de inoculaciones en el cobayo.
4. La neutralización de los ejemplares gástricos permitirá que el bacilo tuberculoso viva varios días si no pueden examinarse los ejemplares en el acto.

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